[4 + 2] CYCLOADDITIONS OF IMINOACETONITRILES: SYNTHESIS OF HIGHLY SUBSTITUTED TETRAHYDROPYRIDINES AND INDOLIZIDINE ALKALOIDS

By

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Purdue University, 2008

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

SEPTEMBER 2013

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Acknowledgments

I would like to begin by thanking my thesis advisor, Rick Danheiser, for being extremely supportive throughout my entire graduate career. His love for teaching and his continuous encouragement kept me motivated to improve as a chemist. He has also been extremely patient and supportive with me constantly changing my mind about career goals. I would also like to thank Tim Jamison for our discussions about chemistry and my life goals.

I would also like to acknowledge my close friend, mentor, and subgroup partner Shaun Fontaine. He not only taught me the lab technique to be successful with my research, but how working with a best friend can be so rewarding. I would also like to acknowledge the other past IAN subgroup members who contributed great ideas and work to make my time here so pleasant.

I owe thanks to the other members of the Danheiser laboratory, especially Tom Willumstad, for a great work environment. Tom was a great friend for 5 years and was always there to talk about almost anything. I am pretty sure we laughed every day about something. To Phil Hamzik, thank you so much for being a great "desk neighbor" for three years. You never cease to amaze me with your views on the world, fear of your own blood, and fear of bugs.

Thanks to my MIT friends who made the last 5 years a blast, especially Todd, Jeremy, and my CGSC friends. I would like to thank Alyssa Larson for being an amazing friend since the day Jeremy introduced us at orientation. Most of my favorite memories of graduate school included her. I am so sad that we will be living 1000 miles apart, but we have many girl's weekends in our future.

I would like to thank my parents, Richard and Eileen, for putting their daughters before everything else to insure we received the best education and grew up in the perfect little family. They spent countless hours at violin lessons, sporting events, and traveling around the country to ensure we were well rounded and exposed to many new things. Most of my success is because of my parents, and because of that I owe them a debt of gratitude. I would also like to thank my big sister Lynn for being an excellent role model and pushing me to come out of my shell and pursue my dreams.

Finally I would like to thank my husband Mitch for supporting me for the past five years even though we were living at a distance from one another. He has been patient not living with his wife for our first year of marriage so I could finish my PhD, and for that I will be forever grateful. I cannot begin to explain how excited I am to start our exciting life together.

To mom, dad,
Mitch, and Lynn

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Submitted to the Department of Chemistry
on July 1, 2013 in partial fulfillment of the
requirements for the degree of Doctor of Philosophy

ABSTRACT

Iminoacetonitriles participate as activated imino dienophiles in intermolecular and intramolecular aza Diels-Alder reactions affording tetrahydropyridines and indolizidines. The α-amino nitrile cycloadducts are versatile synthetic intermediates that participate in a variety of stereoselective transformations to further elaborate the six-membered ring. This thesis describes the scope of the intermolecular [4 + 2] cycloaddition of *N*-benzyliminoacetonitrile with unactivated and activated dienes, as well as, the synthetic elaboration of the cycloadducts. This thesis also describes the worked performed to complete the total syntheses of indolizidines (-)-235B', (-)-235B", and (+)-235B" using the aza Diels-Alder reaction of an iminoacetonitrile as the key step.

Thesis Supervisor: Rick L. Danheiser

Title: Arthur C. Cope Professor of Chemistry

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Part I

Introduction and Background

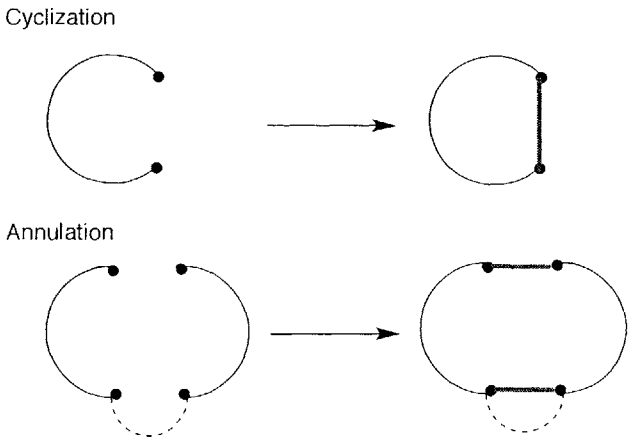
Chapter 1

Aza Diels-Alder Cycloadditions of Imino Dienophiles

Introduction: Cyclization and Annulation Strategies

Ring systems appear in a vast number of pharmaceutical agents and natural products. A primary focus of research in our laboratory is the development of reliable and efficient routes to cyclic and polycyclic molecules. There are two general strategies for the construction of ring systems (Scheme 1). A cyclization strategy involves the intramolecular generation of one new bond, whereas an annulation strategy involves the formation of two new bonds in either an intermolecular or intramolecular fashion to form a new cyclic structure.[1] Annulation strategies are more convergent strategies due to the formation of two new bonds, generally making them more powerful strategies for the synthesis of cyclic compounds. The intramolecular variant of an annulation strategy results in the formation of polycyclic systems. Both intermolecular and intramolecular annulations have the potential for setting several stereocenters in a single step, adding to the appeal of this strategy.

Scheme 1



[1] For a definition of annulation, see Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670- 7672.

Synthesis of Six-Membered Ring Systems via [4 + 2] Cycloadditions

The development of efficient methods for constructing substituted six-membered nitrogen-containing heterocycles has been the subject of extensive research because of the vast number of natural products and pharmaceutical agents containing these ring systems. The Diels-Alder reaction, an annulation strategy, was first reported by Otto Diels and Kurt Alder,[2] and quickly became one of the most powerful methods in organic synthesis for the construction of six-membered ring systems. The Diels-Alder reaction[3] can set several stereocenters around the new ring and can tolerate a wide variety of functional groups on both the dienophile and diene. Incorporation of a nitrogen atom in either the 4π or 2π component (the aza Diels-Alder reaction[4,5]) provides access to six-membered nitrogen containing heterocycles with many of the same advantages associated with the all carbon version of the reaction (Scheme 2).[6]

---

[2] Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98-122.

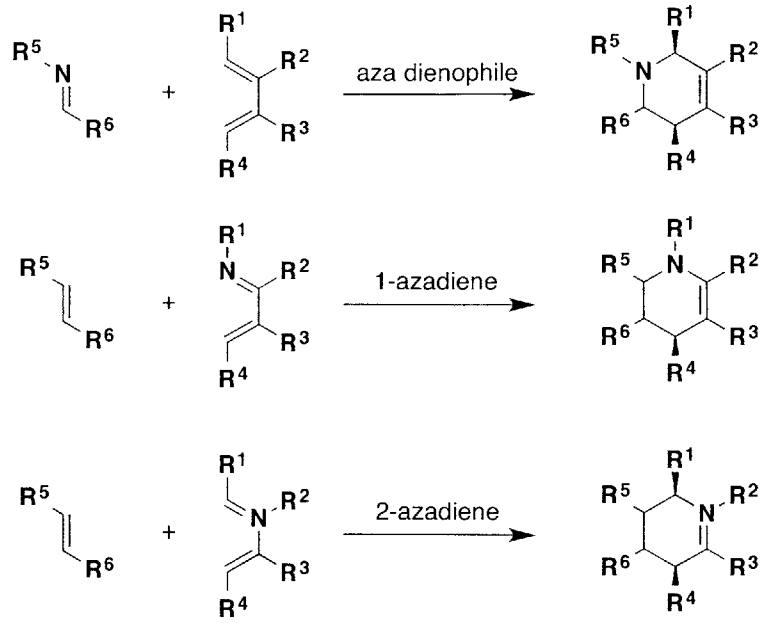
[3] For reviews of the Diels-Alder reaction, see: (a) Onishchenko, A. S. *Diene Synthesis* Israel Program for Scientific Translations, Jerusalem, 1964. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990. (c) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction: Selected Practical Methods*; John Wiley & Sons: New York, 2002. (d) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons: New York, 1990. (e) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 315-399.

[4] For reviews of the aza Diels-Alder reaction, see: (a) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902-923. (b) Memeo, M. G.; Quadrelli, P. *Chem. Eur. J.* **2012**, *18*, 12554-12582. (c) Rowland, G. B.; Rowland, E. B.; Zhang, Q.; Antilla, J. C. *Current Organic Chemistry*, **2006**, *10*, 981-1005. (d) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. *Org. React.* **2005**, *65*, 141-599. (e) Buonora, O.; Olsen, J-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099-6138. (f) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1-120. (g) Waldmann, H. *Synthesis*, **1994**, 535-551. (h) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 401-449. (i) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987.

[5] For mechanistic models of intramolecular hetero-Diels—Alder reactions, see: Iafe, R. G.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 2679-2686.

[6] For a review on all-carbon and hetero Diels-Alder reactions, see: Ishihara, K.: Sakakura, A. [4 + 2]-Cycloaddition Reactions. In *Science of Synthesis, Stereoselective Synthesis*; Evans, P. A., Ed.; Georg Thieme Verlag; Stuttgart, Germany, 2011, Vol. 3, pp 67-123.

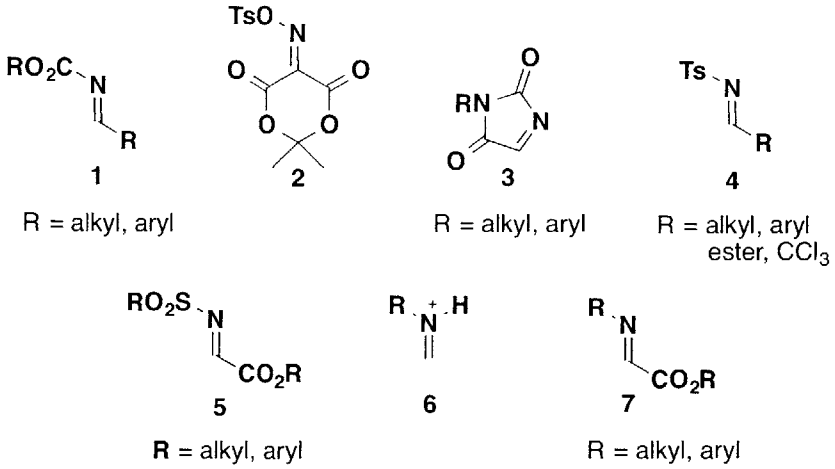
Scheme 2



Intermolecular [4 + 2] Cycloadditions of Imino Dienophiles

The use of imino dienophiles as 2π components in [4 + 2] cycloadditions continues to be the primary focus of many research groups. Imino Diels-Alder (ImDA) reactions generate hydropyridines with a variety of substitution patterns via the combination of imines or iminium ions with conjugated dienes containing a wide array of functional groups. Electron-deficient imines are more reactive in aza Diels-Alder reactions and Scheme 3 shows several classes of the most common imino dienophiles reported in the literature.

Scheme 3



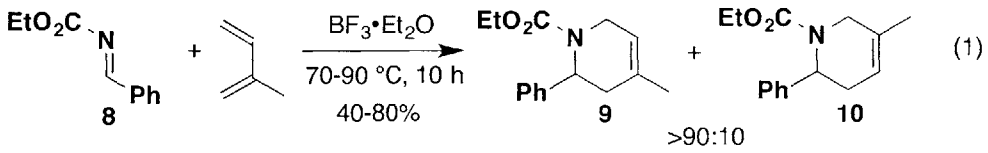
N-Acyl Imines in [4 + 2] Cycloadditions

N-Acyl imines, such as **1**[7] and **3**[8], comprise one of the most well-studied classes of imines for aza Diels-Alder reactions. These electron-deficient imines react with both unactivated dienes (i.e., alkyl-substituted dienes) and activated dienes (i.e., Danishefsky-type dienes), and with high regioselectivity in cases where unsymmetrical dienes are employed. In reactions with cyclic dienes, the exo-product with respect to the substituent on carbon (i.e., R in **1**) is often observed with high selectivity. However, depending on the substituent, the selectivity can be poor and in some cases the endo cycloadduct is preferred. If the substituent is bulky, it may interfere with the developing one-carbon bridge in the transition state when the N-acyl group is endo, resulting in the formation of cycloadduct where the substituent is endo. The use of N-acyl imines in [4 + 2] cycloadditions generally requires elevated temperatures or the addition of Lewis acids such as $BF_3 \bullet Et_2O$ to increase reactivity. The reaction of isoprene and N-acyl imine **8** in the presence of a Lewis acid at elevated temperatures is highly regioselective for **9**.[7a] In

[7] For examples of acyclic *N*-acyl imine dienophiles, see: (a) Merten, R.; Müller, G. *Chem. Ber.* **1964**, *97*, 682-694. (b) Imagawa, T.; Sisido, K.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2922-2924. (c) Krow, G. R.; Henz, K. J.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 1888-1894.

[8] For examples of cyclic *N*-acyl imine dienophiles, see: (a) Goldstein, E.; Ben-Ishai, D. *Tetrahedron Lett.* **1969**, *10*, 2631-2634. (b) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119-3127. (c) Edwards, O. E.; Greaves, A. M.; Sy, W.-W. *Can. J. Chem.* **1988**, *66*, 1163-1172.

general, reactions of N-acyl imines consistently proceed with high regioselectivity (>9:1), an advantage of this class of imines.



(1)

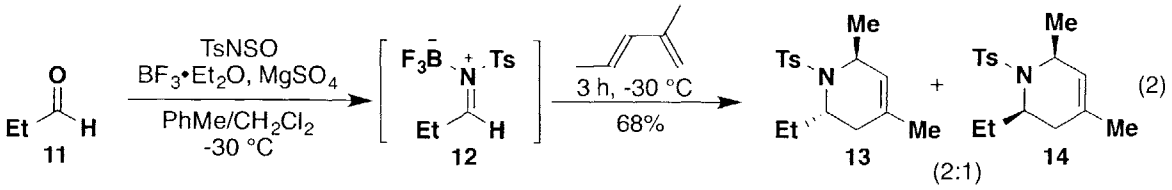
N-Sulfonyl Imines in [4 + 2] Cycloadditions

In general, N-sulfonyl imines[9] of type **4** react with acyclic dienes in ImDA reactions with low stereoselectivity, although in some cases good selectivity is observed depending on the substituents on the diene. The regioselectivity of reactions of N-sulfonyl imines in [4 + 2] cycloadditions with unsymmetrical dienes is excellent and products are easily predicted based on a dipolar mechanistic model. Like N-acyl imines, this class of imino dienophiles requires the presence of Lewis acids or elevated temperatures for successful Diels-Alder reactions.

In 1989, Weinreb reported the generation of N-sulfonyl imines in situ from enolizable aldehydes, and the subsequent trapping of these imines with 1,3-dienes in a one-pot process, all in the presence of $BF_3•Et_2O$.[10] Addition of magnesium sulfate or 4 Å molecular sieves resulted in higher reproducible yields. As illustrated in eq 2, poor diastereoselectivity is a limitation of this method. Reaction of 2-methyl-1,3-pentadiene affords a 2:1 mixture of the 2,6-*trans* (**13**) and 2,6-*cis* tetrahydropyridines (**14**) in moderate yield. Reaction of 2,4-hexadiene resulted in a 1:1 mixture of diastereomers.

[9] For examples of *N*-sulfonyl imine dienophiles, see: (a) Kresze, G.; Albrecht, R. *Chem. Ber.* **1964**, *97*, 490-493. (b) Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431-1434. (c) Fujii, T.; Kimura, T.; Furukawa, N. *Tetrahedron Lett.* **1995**, *36*, 4813-4816.

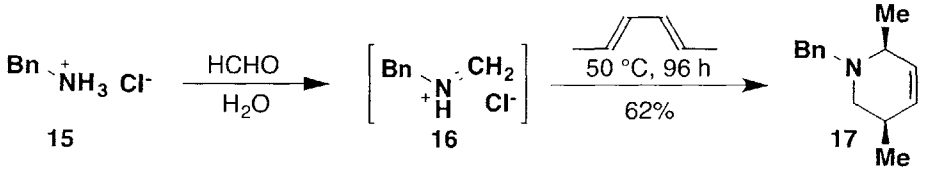
[10] Sisko, J.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3037-3040.



(2)

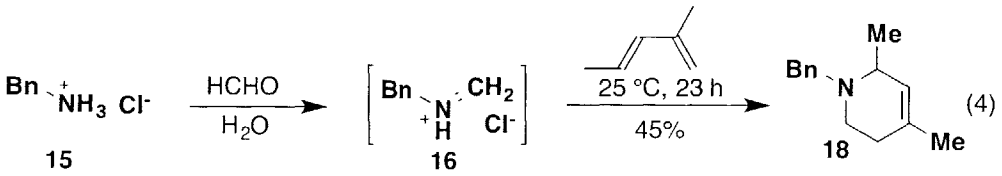
Formiminium Ions in [4 + 2] Cycloadditions

In 1985, Larsen and Grieco first reported the reaction of formiminium ions (**6**) in [4 + 2] cycloadditions under mild aqueous conditions.[11] Primary amine hydrochlorides react with formaldehyde to form iminium salts that participate in cycloadditions with a variety of dienes in a one-pot process. As shown in eq 3, the reaction with 2,4-hexadiene forms only one diastereomer (**17**), suggesting that the mechanism of the cycloaddition is concerted and asynchronous rather than involving a stepwise, ionic process.



(3)

Grieco also observed excellent regioselectivity in cases where 2-methyl-1,3-pentadiene (eq 4) and isoprene were the participating dienophiles. Only one regioisomer was observed and isolated in each case, albeit in moderate yield. An advantage to this method is the mild reaction conditions (25-55 °C) involved in the cycloadditions of simple unactivated dienes.



(4)

[11] (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768-1769. (b) Parker, D. T. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; pp 47-81.

C-Acyl Imines in [4 +2] Cycloadditions

C-Acyl imines (**7**)[12] are another class of activated imines that participate in [4 + 2] cycloadditions. Cycloadditions of this class of aza dienophiles proceed with excellent regioselectivity and in good yield. Most Diels-Alder reactions involving this type of imines require elevated temperatures or acid catalysis. Bailey and coworkers have reported the class of C-acyl imines that are presently the state of the art for reactions with unactivated dienes. In 1989, Bailey and coworkers reported the use of the iminium salt **20** (generated from ethyl glyoxylate (**19**) and benzylamine hydrochloride) with several unactivated dienes to afford cycloadducts in modest yield and high diastereoselectivity (eq 5).[13] Addition of molecular sieves to the reaction mixture in order to facilitate the formation of the imine was detrimental to the outcome of the cycloaddition, proving water has a key role in the reaction. Controlling the amount of water in the reaction mixture is important since high concentrations of water lower the imine concentration by hydrolysis and also result in lower yields. Bailey proposed that water was hydrogen bonding to the imine, preventing rotation to a less reactive conformation (Figure 1). This shows the importance of controlling the amount of water introduced to the reaction mixture for a successful cycloaddition.

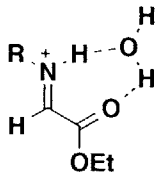
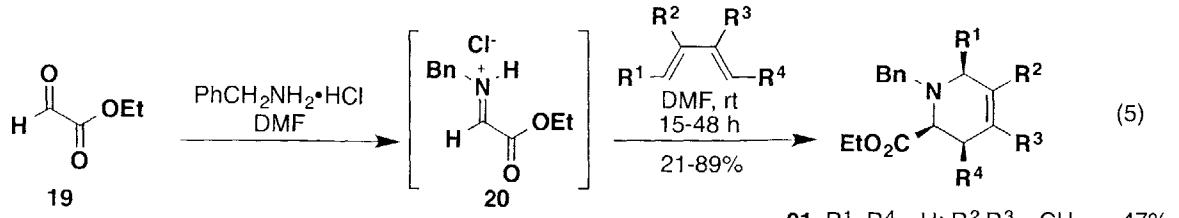


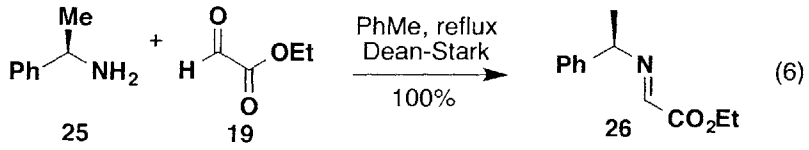
Figure 1

[12] For select examples of *C*-acyl imine dienophiles, see: Lucchini, V.; Prato, M.; Scorrano, G.; Tecilla, P. *J. Org. Chem.* **1988**, *53*, 2251. (b) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707-9718.
[13] Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781-6784.



21 R^1, R^4 = H; R^2 R^3 = CH_3 47%
22 R^1, R^2, R^4 = H; R^3 = CH_3 43%
23 R^2, R^3 = H; R^1, R^4 = CH_3 36%
24 R^2, R^3, R^4 = H; R^1 = CH_3 38%

The development of enantioselective aza Diels-Alder reactions using chiral auxiliaries is another active area of research.[14] In 1991, Bailey and coworkers introduced an asymmetric variant to their method by using a phenylethylimine derivative (**26**).[15] Both (*R*) and (*S*)-1-phenylethylamine are commercially available and imine **26** is synthesized in quantitative yield via a condensation reaction with ethyl glyoxylate (eq 6).



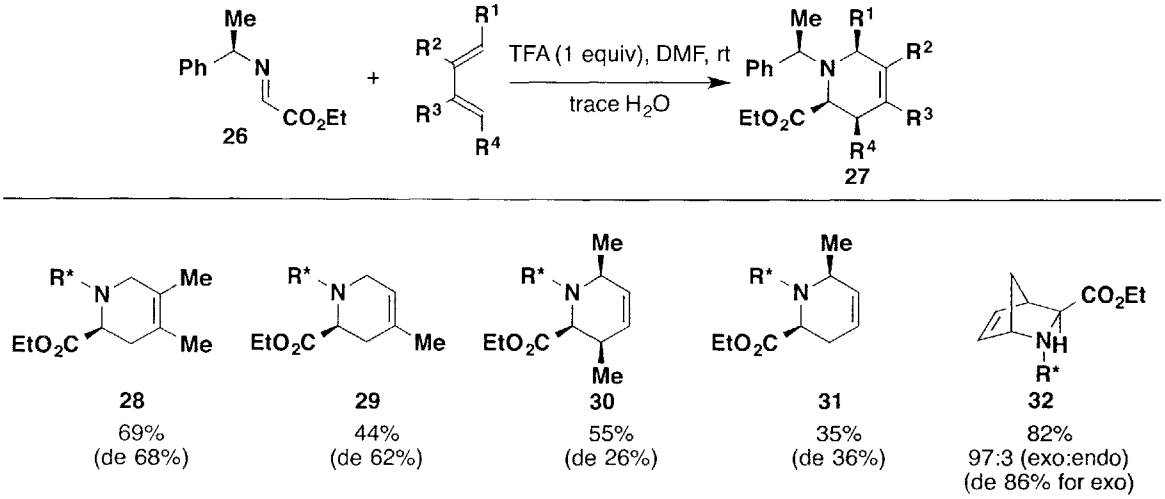
Bailey reported that a variety of unactivated cyclic and acyclic dienes react with **26** to afford single regioisomers in moderate to high yields. Selected examples of cycloadducts are shown in Scheme 4. Tetrahydropyridine **30** was formed as a mixture of diastereomers; however, only the endo carboethoxy product was observed. Use of cyclopentadiene in this [4 + 2] cycloaddition results in a higher yield and excellent exo selectivity (97:3) as expected with this

[14] For selected examples of ImDA reactions using chiral auxiliaries, see: (a) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261-4263. (b) Hamley, P.; Helmchen, G.; Holmes, A. B.; Marshall, D. R.; MacKinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1992**, 786-788. (c) Barluenga, J.; Aznar, F.; Valdés, C.; Martin, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403-4404. (d) Barluenga, J.; Aznar, F.; Cristina, R.; Valdés, C.; Fernández, M.; Cabal, M-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805-811. (e) Badorrey, R.; Cativila, C.; Diaz-de-Vilegas, M. D.; Galvez, J. A. *Tetrahedron Lett.* **1997**, *38*, 2547-2550.

[15] (a) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1337-1340. (b) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263-1282.

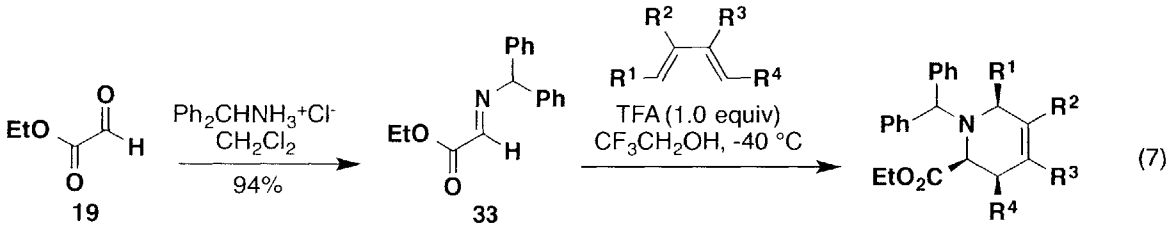
reactive diene. Note that the reaction of cyclopentadiene with the less substituted benzylimine derivative **20** resulted in poor exo:endo selectivity (69:31). The difference may be due to the greater steric effect of the phenylethyl group interacting with the developing one-carbon bridge in the transition state, setting a preference for a transition state with the *N*-benzylethyl group endo.

Scheme 4



Although 1-phenylethylimine **26** showed good reactivity with a variety of unactivated dienes, the asymmetric induction with this particular chiral auxiliary was not high in the case of acyclic dienes. Bailey and coworkers discussed how the endo orientation of the ester group results in the chiral auxiliary being relatively far from the diene in the transition state. In the case of **28**, it was surprising that the asymmetric induction was as high as it was. Although the dr in this case was higher than expected, the low to moderate yields suggested improvements were still needed to make this method more attractive.

In a later report,[16] Bailey addressed many of the problems with his first two methods (i.e., the methods based on benzylimine **20** and phenylethylimine **26**). The low and variable yields observed in many of the cycloadditions were attributed to the stability and purity of the imines. Bailey noted that his acyl imino dienophiles readily react with nucleophiles such as benzylamine, which is present in the reaction that generates the imine. Side reactions of the electron-deficient imine with nucleophiles were observed under the reaction conditions lowering the yield of the cycloadduct product. Bailey and coworkers therefore subsequently developed a new imine derived from benzhydrylamine (**33**) that can be purified to afford an indefinitely stable solid. The stability and purity of this new imine led to an improvement in the yields of the cycloaddition in all cases as shown in eq 7.



(7)

34	R^1, R^4 = H; R^2 R^3 = CH_3	95%
35	R^1, R^2, R^4 = H; R^3 = CH_3	87%
36	R^2, R^3 = H; R^1, R^4 = CH_3	60%
37	R^2, R^3, R^4 = H; R^1 = CH_3	62%
38	R^3, R^4 = H; R^1, R^2 = CH_3	42%

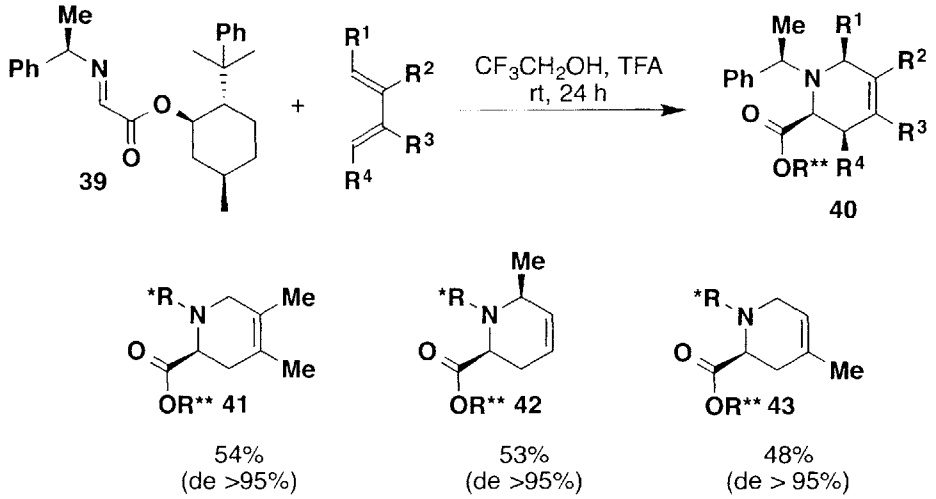
In 1994, Bailey partnered with Holmes to further improve the stereoselectivity of the method by incorporating an 8-phenylmenthyl auxiliary as the ester portion of the dienophile.[17] Previously, Holmes had used *N*-tosyl imino esters of type **5** bearing a chiral auxiliary within the

[16] Bailey, P. D.; Smith, P. D.; Pederson, F.; Clegg, W.; Rosair, G. M.; Teat, S. J. *Tetrahedron Lett.* **2002**, *43*, 1067-1070.

[17] Bailey, P. D.; Londesbrough, D. J.; Hancox, T. C.; Heffernan, J. D.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2543-2544.

ester and observed ca. 75% asymmetric induction.[18] Pairing the two chiral groups on the imine result in very high asymmetric induction when the two auxiliaries are matched. Scheme 5 shows selected cases of the double auxiliary approach reported by Bailey and Holmes. Use of (*R*)-phenylethyl imine resulted in a matched case with high de (>95%), while the use of the mismatched (*S*)-phenylethyl as the *N*-auxiliary eroded the de significantly (0 to 82%).

Scheme 5



The methods developed by Bailey and coworkers demonstrate the high reactivity of C-acyl imines with acyclic unactivated dienes. The optimization of this method resulted in moderate to high yields, high diastereoselectivity, high regioselectivity, and high asymmetric induction for these [4 + 2] cycloadditions. However, it is important to note the limitations of this method. Many natural products and targeted pharmaceutical agents have a trans relationship between the C2 and C6 substituents on the piperidine ring system. The method presented here has excellent selectivity for cis-2,6-substituted systems, but the corresponding trans isomers are not attainable. This method also installs an ester at the C2 position that cannot be easily

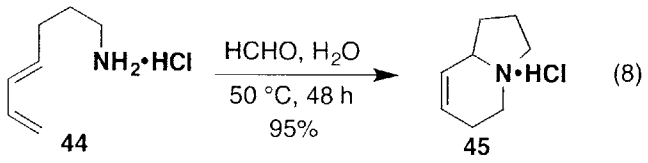
[18] Hamley, P.; Helmchen, G.; Holmes, A. B.; Marshall, D. R.; MacKinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1992**, 786-788.

manipulated into other groups in a few steps. These limitations leave room for improvement or the discovery of an alternative efficient aza Diels-Alder approach to the synthesis of highly substituted six-membered nitrogen heterocycles.

Intramolecular [4 + 2] Cycloadditions of Imino Dienophiles

Many of the imino dienophiles that participate in *inter*molecular [4 + 2] cycloadditions also are reported to take part in *intra*molecular cycloadditions.[3d,11,19] To date there are far fewer examples of intramolecular aza Diels-Alder reactions than of the intermolecular variant. This section will provide an overview on the current state of the art with regard to intramolecular cycloadditions of imino dienophiles.

Grieco and coworkers studied an intramolecular variant of their unactivated iminium salt method, and applied it in the total syntheses of several alkaloids including (±)-lupinine, (±)-julandine, (±)-dihydrocannivonine, and (-)-8a-epipumiliotoxin C.[11,19a-b] This work demonstrated that iminium ions are excellent dienophiles in not only intermolecular cycloadditions but also intramolecular aza Diels-Alder reactions. In 1985, Grieco reported the cycloaddition of (*E*)-4,6-heptadienylamine hydrochloride in 37% aqueous formaldehyde to produce **45** in 95% yield. Later, Grieco introduced another intramolecular process where a dienyl aldehyde is condensed with *N*-benzylamine.[10]

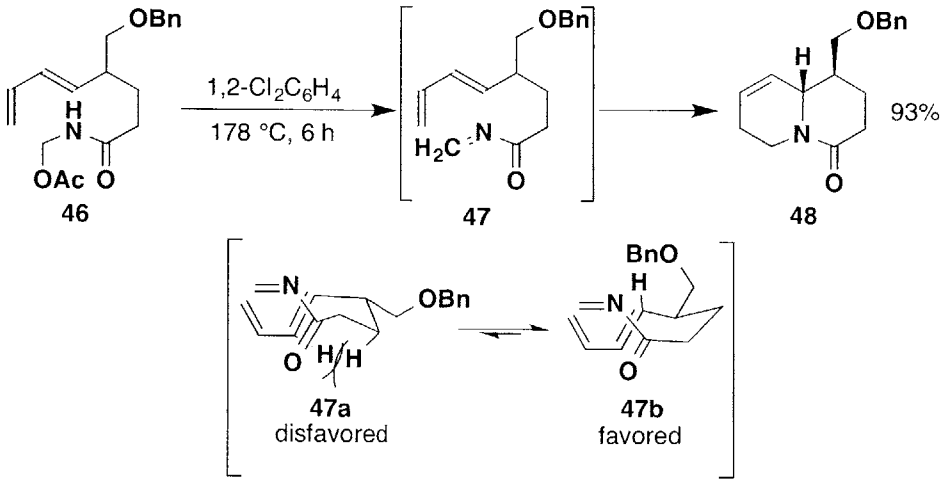


44 45 (8)

[19] For selected examples of intramolecular aza Diels-Alder reactions, see: (a) Earl, R. A.; Vollhardt, K. P. C. *Heterocycles* **1982**, *23*, 265. (b) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325-3330. (c) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658-3662.

N-Acyl imines are one of the most well known classes of dienophiles that participate in intramolecular aza Diels-Alder reactions. Generally the imines are generated in situ via a thermolysis reaction because in many cases N-acyl imines are not bench stable and cannot be isolated cleanly. Bremmer and Weinreb used this strategy in a synthesis of epi-lupinine.[20] Diene **46** was synthesized in seven steps from commercially available methyl sorbate and then heated in refluxing *o*-dichlorobenzene for 6 h. The resulting imine (**47**) participates in an intramolecular [4 + 2] cycloaddition with the tethered diene to furnish lactam **48** in 93% yield. The cycloaddition most likely proceeds via transition state **47b** where the N-acyl group adopts the endo conformation and the benzyloxymethyl group has a pseudoequatorial orientation on the developing six-membered ring. One would expect the chair-like transition state of **47a** to be favored over the boat-like transition state in **47b**, however, the non-bonding interactions between the hydrogen on the diene and the pseudo-axial hydrogen on the tether result in a less favorable transition state. The predicted stereochemistry that would result from transition state **47a** was not observed after a comparison of the quinolizidine cycloadduct to natural lupinine.

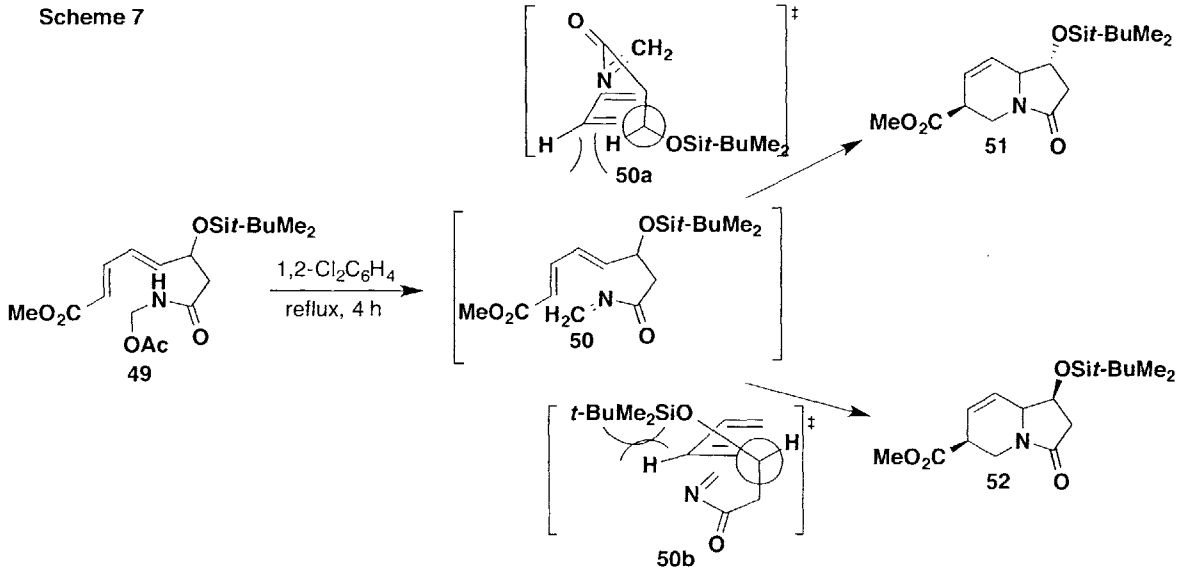
Scheme 6



[20] Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, 24, 261-264

Weinreb et al. also used this method for the construction of indolizidine ring systems by synthesizing a substrate with a shorter tether between the diene and imine.[21] Unfortunately, the stereoselectivity observed in the indolizidine case was not as high as for quinolizidines. Reaction of **49** afforded a 64:36 mixture of **51** and **52** in 82% yield. In both potential transition states, non-bonding interactions occur when the acyl group is in an endo orientation, resulting in a smaller energy difference between the transition states and poor stereoselectivity for the transformation.

Scheme 7



Weinreb also examined incorporating a C-acyl group on the N-acyl imine, and interesting stereochemical features were observed in reactions of these N-C-diacyl imine systems.[22] Again, thermolysis revealed an imine (**54**) that underwent an aza Diels-Alder reaction to provide one product (**55**) in 83% yield. The preferred transition state **54** puts the *N*-acyl group endo and the pentyl substituent in a pseudoequatorial position.

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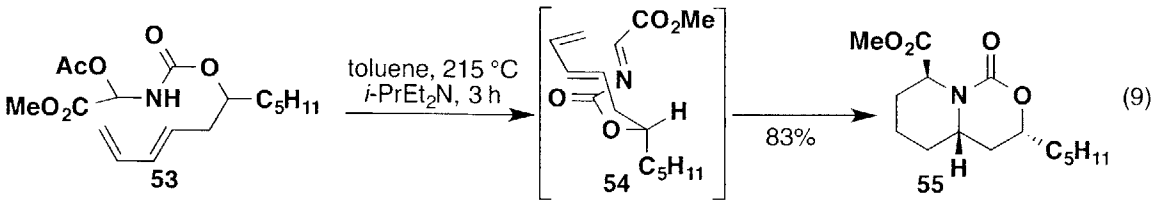
[21] Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065-7068.

[22] (a) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153-1155. (b) Nader, B.; Bailey, T. R.; Ranck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573-7580. (c) Bland, D. C.; Raudenbush, B. C.; Weinreb, S. M. *Org. Lett.* **2000**, *2*, 4007-4009.



(9)

In summary, the intramolecular aza [4 + 2] cycloaddition has received considerably less attention than the intermolecular variant. Grieco and Weinreb were able to show the utility of such a method in the synthesis of several natural products, but there remains much work to be done in the area of intramolecular cycloadditions of imino dienophiles.

Enantioselective [4 + 2] Cycloadditions of Imino Dienophiles using Chiral Catalysts

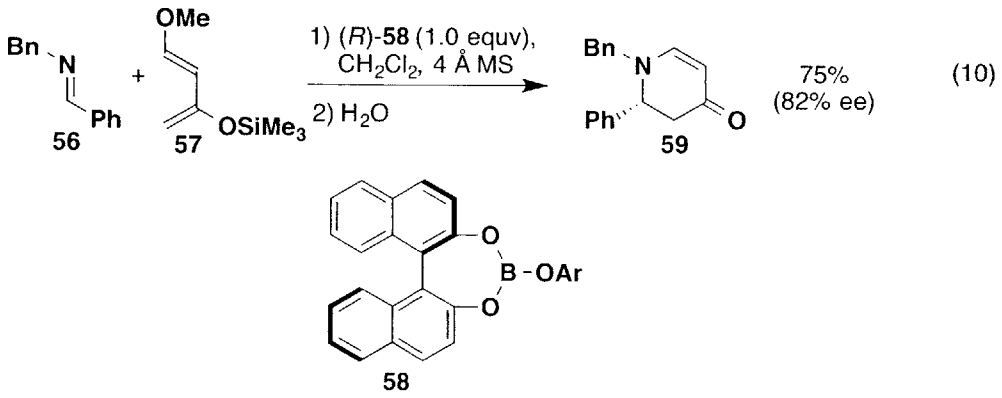
The development of an asymmetric variant of the aza Diels-Alder reaction is an important problem because of the importance of accessing chiral pharmaceutical agents and natural products. As discussed in the previous section, a number of methods are available based on the use of chiral auxiliaries on either the dienophile or diene. The use of chiral catalysts or promoters in [4 + 2] cycloadditions to access chiral six-membered heterocycles is another active area of research and is highlighted in this section.

Although asymmetric catalysis of hetero Diels-Alder reactions has been known for many years,[23] it was not until recently that the method was applied to reactions of imino dienophiles. There are several important features of imines and the cycloadducts that make it difficult to optimize catalytic methods. Strong catalyst coordination to the imine and resulting cycloadduct slows down the turnover for the catalyst, and often a stoichiometric amount of Lewis acid is necessary. The facile E/Z-isomerization of imines is also often a complication and often allows

[23] For a review on asymmetric hetero-Diels-Alder reactions, see: Pellissier, H. *Tetrahedron* **2009**, *65*, 2839-2877.

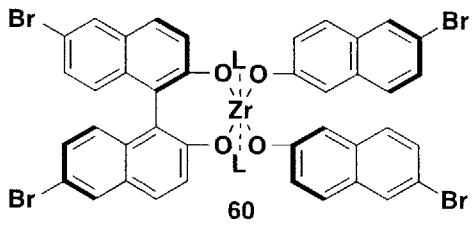
the imine-Lewis acid complex to adopt several conformations in solution. Finally, imines synthesized from enolizable aldehydes have the tendency to form enamines rather than participating in [4 + 2] cycloadditions. These special features and challenges of imino dienophiles are the reason there are relatively few effective methods developed to date.

Chiral boron reagents were some of the first chiral catalysts used in ImDA reactions.[24] Eq 10 shows *C*-phenyl-*N*-benzylimine (**56**) reacting with Danishefsky's diene in the presence of a stoichiometric amount of chiral boron Lewis acid (**58**) to yield piperidone **59** in 75% yield and high enantiomeric excess (91:9 er). Similar reactions with Danishefsky-type dienes reported in this paper result in high yields with enantiomeric ratios as high as 95:5; however, at least one equivalent of both the chiral boron reagent and activated diene are required in these particular cycloadditions. Several other examples of boron promoted cycloadditions are reported in the literature including examples using chiral auxiliaries on the imine.[25]



[24] Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264-3265.
[25] (a) Hattoi, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749-1760 (b) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Tamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520-10524

Another useful catalyst for enantioselective ImDA reactions is based on zirconium (IV) Lewis acids. This approach was pioneered by Kobayashi in 1998 using **60**[26] to promote the reaction of N,C-diaryl imines and Danishefsky's diene.[27] Yields and enantioselectivities vary with different solvent, ligand, and substrate, but the optimized conditions resulted in high yields (72-98%) and 82:18 to 97:3 er. Kobayashi later developed new chiral zirconium catalysts for the promotion of similar aza Diels-Alder reactions with benzoylhydrazones and C-alkylimines.[28] A limitation to this method and many other methods involving chiral organometallic reagents[29] is the requirement that only highly activated Danishefsky-type dienes participate in the reaction.



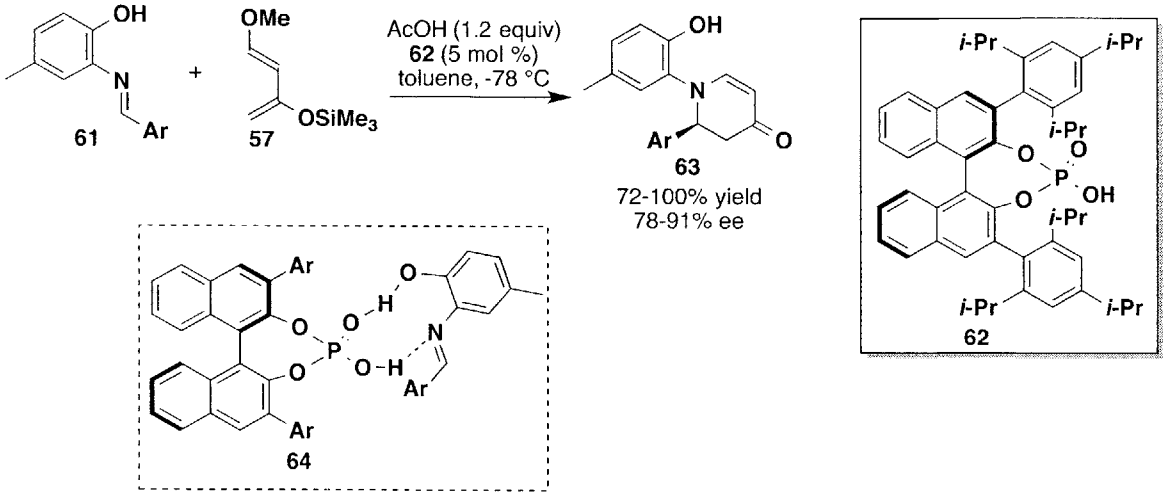
60

A class of chiral aza Diels-Alder reaction promoters that is of particular interest to our group is Brønsted acids[30] and in particular BINOL phosphoric acids. Akiyama and coworkers reported the first use of chiral phosphoric acids derived from (*R*)-BINOL in cycloadditions of *N*-aryl aldimines of type **61** with Danishefsky's diene. [31] They discovered that *(R)*-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate ((*R*)-TRIP, **62**) was superior to

[26] Lewis acid **60** is generated from Zr(O*t*-Bu)$_4$ and two equivalents of (*R*)-6, 6'-dibromo-1,1'-binaphthol.
[27] Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 979
[28] (a) Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225-1227. (b) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803-1806.
[29] For select examples of enantioselective ImDA reactions with chiral Zr, Cu, Ag catalysts, see: (a) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558-3588. (b) Newman, C. A.; Antilla, J. C.; Chen, P.; Predeus, A. V.; Fielding, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7216-7217. (c) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456-457. (d) Josephsohn, N. S.; Snapper, M. L; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018-4019.
[30] Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744-5758.
[31] Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141-143.

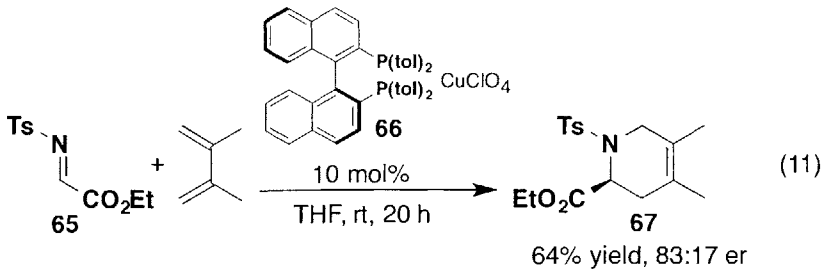
the 3,3'-bisphenyl and 3,3'-bis-*p*-nitrophenyl acids. The transition state complex (**64**) shows the important role of the phenolic hydroxyl group in the coordination of the chiral acid to the imine.

Scheme 8



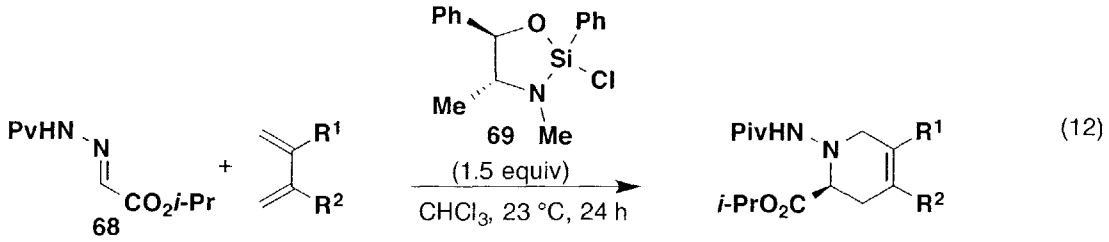
One of the limitations of the enantioselective aza Diels-Alder reactions discussed above is the poor reactivity of unactivated dienes. To date, almost all enantioselective [4 + 2] cycloadditions of aza dienophiles require highly reactive dienes (i.e., Rawal's diene, Danishefsky-type dienes, etc.). Jørgensen developed the first method for an enantioselective aza Diels-Alder reaction with an unactivated diene. Imine **65** reacts with 2,3-dimethylbutadiene, catalyzed by a 10 mole% of **66**, to afford cycloadduct **67** in 64% yield and 83:17 er (eq 11).[32] This was the only example of a reaction with an unactivated diene reported by Jørgensen.

[32] (a) Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547-2548. (b) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435-2448.



(11)

In 2010, Leighton and coworkers reported the use of a chiral silicon Lewis acid to promote aza Diels-Alder reactions of non-Danishefsky-type dienes.[33] The use of C-acyl and aliphatic alkyl hydrazones resulted in good yields (>66%) and excellent enantioselectivity (>81% ee). Eq 12 shows selected examples from this work. The silicon Lewis acid must be used in excess to achieve high reactivity and high enantioselectivity; however, pseudoephedrine can be recovered in 93% yield and can be reused. C-Aliphatic hydrazones are also reactive dienophiles, although higher temperatures and longer reaction times are often needed due to the reduced reactivity in the absence of a C-acyl group.



(12)

70	$R^1 = CH_3$; $R^2 = CH_3$	91% (85% ee)
71	$R^1 = H$; $R^2 = CH_3$	96% (85% ee)
72	$R^1 = H$; $R^2 = CH_2CH_2Ph$	99% (87% ee)
73	$R^1 = H$; $R^2 = CH_2CH_2OPMB$	95% (90% ee)
74	$R^1 = H$; $R^2 = p\text{-}BrC_6H_4$	70% (98% ee)

In summary, the aza Diels-Alder reaction is a powerful strategy for the efficient and stereoselective synthesis of six-membered nitrogen heterocycles. This remains an active area of

[33] Tambar, U. K.; Lee, S. K.; Leighton, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 10248-10250.

research because of the need for methods that would provide access to a wider variety of substitution patterns on the ring system, as well as to provide enantioselective routes for the synthesis of biologically active natural products and pharmaceuticals.

Chapter 2

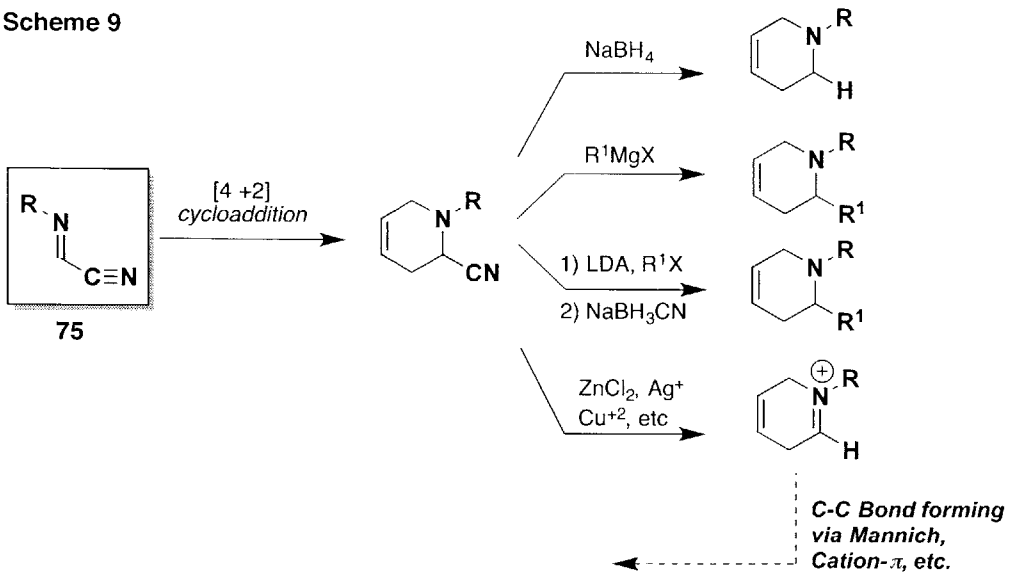
Iminoacetonitriles: Background

Our laboratory has previously investigated cycloadditions of conjugated enynes. As part of these studies we became interested in employing activated imines as 2π components in these cycloadditions.[34] In the course of these studies, Adam Renslo investigated the chemistry of iminoacetonitriles, a new class of electron-deficient imines, which were not previously known to participate in cycloadditions including aza Diels-Alder reactions.

Iminoacetonitriles (**75**) were expected to function as activated dienophiles due to the nitrile electron-withdrawing group and to participate in [4 + 2] cycloadditions with conjugated dienes to afford synthetically useful α-amino nitrile cycloadducts (Scheme 9). α-Amino nitriles can undergo a number of transformations to provide products with valuable functionality. Metalation with LDA or LiHMDS allows further functionalization of the ring system via alkylation with a variety of electrophiles. An iminium ion revealed when the α-amino nitrile is exposed to Lewis or Brønsted acids can be intercepted with Grignard reagents or organosilanes. These iminium ions can also participate in Mannich reactions and other types of "cation-π" cyclization processes.

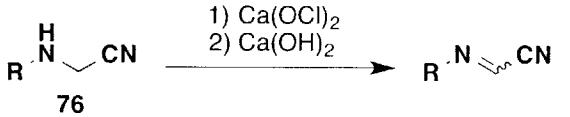
[34] For details, see: Renslo, A. R. I. New Cycloadditions for the Synthesis of Nitrogen Heterocycles. II. Organic Synthesis in Supercritical Carbon Dioxide. Ph.D. Thesis. Massachusetts Institute of Technology, Cambridge, MA, June 1998.

Scheme 9



Synthesis of Iminoacetonitriles

Boyer and Dabek first reported the synthesis of an iminoacetonitrile in 1970, using the reaction of *N*-*t*-butylaminoacetonitrile and *t*-butyl hypochlorite followed by dehydrochlorination with triethylamine. This two-pot procedure produced *N*-*t*-butyliminoacetonitrile in 46% yield.[35] In a subsequent publication, Boyer and Kooi reported chlorination of α-amino nitriles (**76**) with $Ca(OCl)_2$ followed by dehydrochlorination with $Ca(OH)_2$ in a two-step process that requires up to 7 days (eq 13).[36] The long reaction times and wide range of yields suggested that improvements to this method would be necessary in order for iminoacetonitriles to be readily and conveniently available.



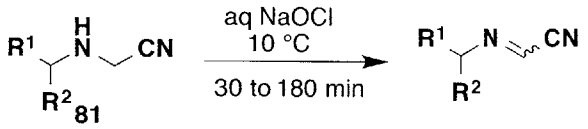
77 R = Me 25%
78 R = Et 50%
79 R = *i*-Pr 72%
80 R = *t*-Bu 76%

(13)

Selva and coworkers recognized the limitations of these prior procedures and improved on Boyer's method by using aqueous sodium hypochlorite in a one-pot procedure to furnish

[35] Boyer, J. H.; Dabek, H. *J. Chem. Soc. D., Chem. Commun.* **1970**, 1204-1205.
[36] Boyer, J. H.; Kooi, J. *J. Am. Chem. Soc.* **1976**, *98*, 1099-1103.

iminoacetonitriles **82-87** in 67-97% yield as a mixture of E/Z imines (eq 14).[37] Two advantages of Selva's procedure are the mild reaction conditions and the shorter reaction time that affords the desired products in good to high yield.



82 R^1 = Me, R^2 = Me	67%	(14)
83 R^1 = Me, R^2 = Et	70%	
84 R^1 = *t*-Bu, R^2 = *t*-Bu	90%	
85 R^1 = Cy, R^2 = Cy	75%	
86 R^1 = Ph, R^2 = H	97%	
87 R^1 = Ph, R^2 = Me	76%	

Our laboratory has employed two general strategies for the synthesis of iminoacetonitriles. The first method involves chlorination of an α-amino nitrile using an approach similar to the one reported by Selva. The second method is a Mitsunobu approach utilizing the reaction of a triflamide and alcohol. The next sections outline the advantages and disadvantages of each of these methods.

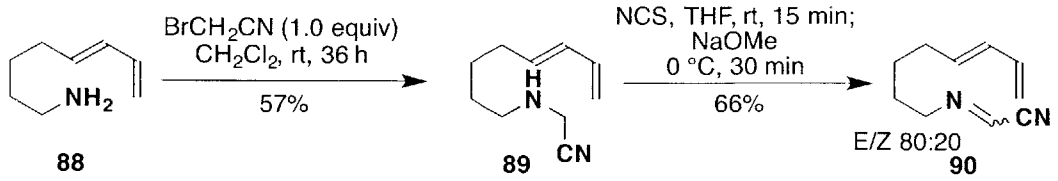
Iminoacetonitriles via N-Chloroaminoacetonitriles

Our laboratory was interested in iminoacetonitriles such as **90** as substrates for studying the intramolecular aza Diels-Alder reaction. Due to the potential reactivity of the diene of this molecule, a chlorinating reagent milder than NaOCl was needed. Former group members Adam Renslo[34] and David Amos[38,39] both worked towards optimizing a one-pot procedure for the formation of iminoacetonitriles from the corresponding α-amino nitrile **89**. Chlorination with *N*-chlorosuccinamide (NCS) followed by the addition of NaOMe facilitated the elimination of HCl and afforded an inseparable 80:20 mixture of E/Z imines **90** in 66% yield (Scheme 10). The

[37] Perosa, A.; Selva, M.; Tundo, P. *Tetrahedron Lett.* **1999**, *40*, 7573-7576.
[38] For details, see: Amos, D. T. Synthesis of Nitrogen Heterocycles via The Intramolecular [4 + 2] Cycloaddition of Iminoacetonitriles. Ph.D. Thesis. Massachusetts Institute of Technology, Cambridge, MA, September 2003.
[39] Amos, D. T.; Renslo, A. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 4970-4971.

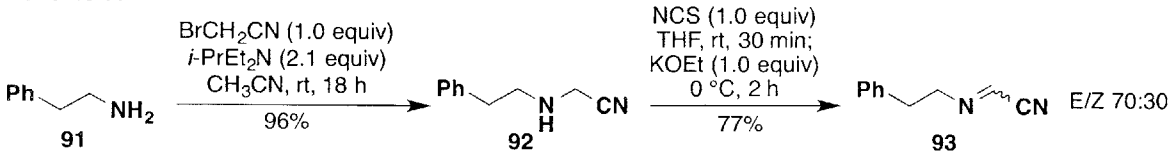
mixture of imines was not significant since it was found that isomerization occurs under the [4 + 2] cycloaddition reaction conditions and both imines react to form the same cycloadducts.

Scheme 10



A slightly modified procedure, developed by Kevin Maloney,[40] resulted in a cleaner elimination of HCl and higher yield of the iminoacetonitriles. Alkylation of *N*-phenylethylamine (**91**) with bromoacetonitrile in the presence of an amine base afforded **92** in excellent yield (96%). Treatment of α-amino nitrile **92** with 1 equiv of NCS at rt for 30 min afforded the *N*-chloroamine. In the same pot, KOEt was added at 0 °C to facilitate dehydrochlorination to furnish iminoacetonitrile **93** in 77% yield as a 70:30 mixture of E/Z isomers. This reaction is clean (by TLC), which results in easier purification and higher yield. Further applications of this method will be discussed in Part II of this thesis.

Scheme 11



Iminoacetonitriles via a Mitsunobu Approach

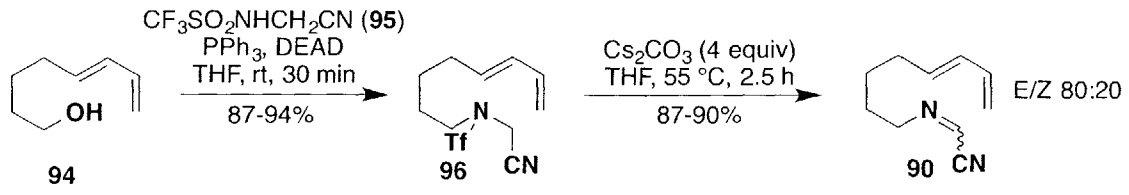
The alkylation of primary amines followed by a one-pot chlorination and elimination of HCl continues to be a valuable method, affording pure iminoacetonitriles in high yield.

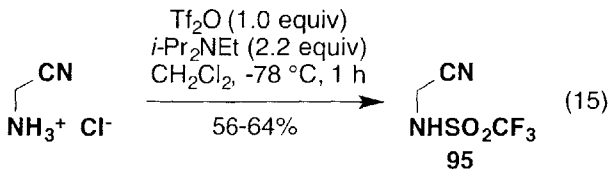
[40] For details, see: Maloney, K. M. [4 + 2] Cycloadditions of Iminoacetonitriles: A General Strategy for the Synthesis of Quinolizidines, Indolizidines, and Piperidines. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, May 2007.

Although this first method developed in our group is reliable, it was recognized that amines are often not as readily available as the corresponding alcohols. In fact, very often the requisite amine is synthesized from the corresponding alcohol via the azide or nitrile that is reduced to the desired primary amine before alkylation with bromoacetonitrile. This strategy adds several steps to any synthetic route, a shortcoming in organic synthesis.

Amos developed a new strategy for iminoacetonitrile synthesis that involves the synthesis of a triflamide via a Mitsunobu reaction with readily available alcohols. Scheme 12 shows the Mitsunobu reaction of commercially available **94** with $CF_3SO_2NHCH_2CN$ **95** (referred to in our laboratory as the "Amos Reagent") to afford triflamide **96** in excellent yield after 30 min. Gently warming a solution of **96** in the presence of excess Cs_2CO_3 eliminates trifluoromethanesulfinate and furnishes the desired iminoacetonitrile **90** in 87-90% yield as an 80:20 mixture of E/Z imines after only a few hours. The "Amos reagent" can be synthesized in one step from inexpensive aminoacetonitrile hydrochloride and triflic anhydride on a 14 g scale (eq 15). Triflamide **95** is a low-melting solid that is stable to storage for months in the refrigerator and under argon. This Mitsunobu method works well with a variety of different alcohols.[38,39]

Scheme 12





(15)

The two methods developed in our laboratory for the synthesis of iminoacetonitriles are both efficient and reliable. As discussed in Part II, we have utilized the first alkylation approach

when synthesizing iminoacetonitriles to participate in intermolecular cycloadditions. For the synthesis of intramolecular cycloaddition substrates, the Mitsunobu approach is usually employed. This includes the iminoacetonitriles used in the quinolizidine and indolizidine natural product syntheses discussed in Part III.[41]

Stereochemical Assignments of Iminoacetonitriles

A mixture of E/Z stereoisomeric imines are produced via both the chlorination/elimination and Mitsunobu/sulfinate elimination routes. From analysis of the ^{1}H NMR spectra, the *E*-imines have been determined to be the major isomers in all cases. The methylene protons (H_B) alpha to the nitrogen are well defined and shifted further downfield for the *Z*-isomer because they lie within the deshielding cone of the nitrile π-bonds. The ^{1}H NMR spectra also reveal a four-bond coupling (^{4}J) between the iminyl proton H_A and the methylene signals in **97** and **98** (Figure 2). This ^{4}J coupling constant provides good evidence for the imine geometry. The *Z*-imine **98** has a transoidal relationship of H_A and the substituent on nitrogen, which produces a larger coupling constant. Aldimines **99** and **100** are well-known imines and show similar ^{4}J couplings as illustrated in Figure 2.[42]

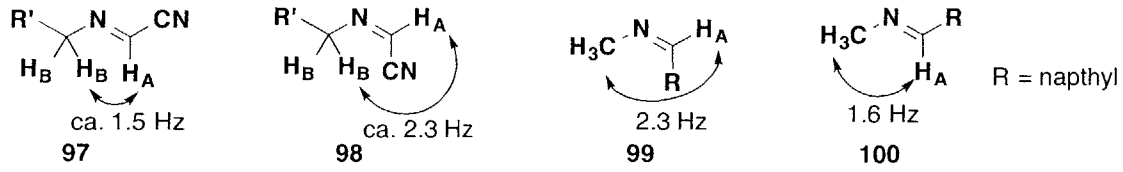


Figure 2

[41] Also see the total synthesis of quinolizidine 217A using iminoacetonitriles: Maloney, K. M.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3115-3118.

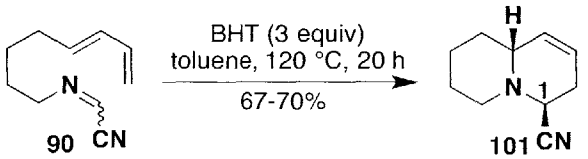
[42] Yeh, H. J. C.; Ziffer, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 2741-2743.

[4 + 2] Cycloadditions of Iminoacetonitriles

As mentioned in the previous section, our laboratory developed two reliable and efficient methods for the synthesis of iminoacetonitriles. This section discusses the finding that this new class of imines are highly reactive 2π components in both thermal and Brønsted acid promoted [4 + 2] cycloadditions with a variety of conjugated dienes.

Thermal [4 + 2] Cycloadditions

In 2003, our laboratory reported the first thermal intramolecular cycloaddition of iminoacetonitriles.[39] For example, diene **90** was found to react in toluene at elevated temperature over a period of 20 h to afford **101** in good yield. BHT is added to the reaction mixture as a radical inhibitor and it was observed that the E and Z isomers of **90** react at similar rates under these reaction conditions.



(16)

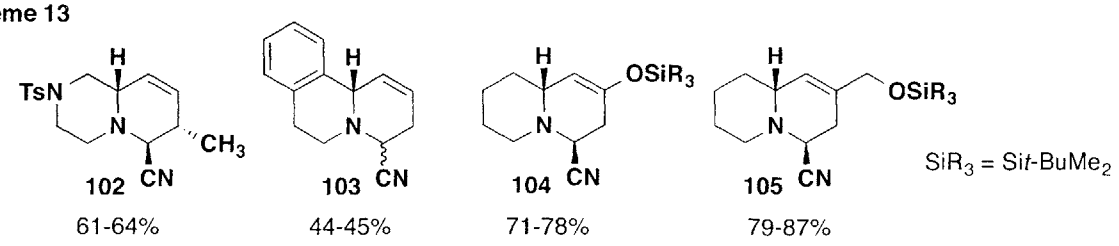
Maloney monitored the same cycloaddition by ^{1}H NMR spectroscopy to further understand the mechanism.[40] Using anisole as an internal standard, he heated the iminoacetonitrile **90** in benzene-d_6 both with and without the addition of BHT. At several time points he determined the amount of starting material and cycloadduct in the reaction mixture via ^{1}H NMR analysis. Maloney determined that the addition of BHT does not have a significant effect on the rate of disappearance of iminoacetonitrile; however, the yield of the reaction does increase by 40% with the addition of BHT. Further NMR experiments showed that the product actually decomposes under the reaction conditions in the absense of BHT. Our hypothesis for the decomposition of the cycloadduct is that a hydrogen atom is lost from the C-1 carbon,

resulting in a carbon-centered radical stabilized by the captodative effect. It was also determined that decreasing the amount of BHT in solution resulted in lower yields. The optimal conditions for thermal cycloaddition reactions continue to involve the presence of 3 equiv of BHT.

These NMR experiments also proved that the E/Z iminoacetonitriles equilibrate under the reaction conditions. Isomerization from an 80:20 mixture to a 60:40 mixture of imines occurs upon heating before the cycloaddition proceeds. The 60:40 ratio of E and Z isomers then remains constant during the course of the cycloaddition. Maloney and Amos observed only one cycloadduct for many of the cases despite the two imines present at the start of the reaction, suggesting that each imine isomer may react to form the same cycloadduct. Alternatively, equilibration of the isomers may be much faster than cycloaddition, which then takes place preferentially via one isomer (Curtin-Hammett effect).

Scheme 13 shows several cycloadducts produced via this thermal [4 + 2] cycloaddition strategy.[39] Thermal cycloadditions tolerate a variety of functional groups such as silyl enol ethers (**104**). Cycloadduct **103** was isolated as a 79:21 mixture of cyano epimers. The two epimers react similarly in the transformations of α-amino nitriles (vide infra), so the isolation of a mixture is not a drawback of this method.

Scheme 13



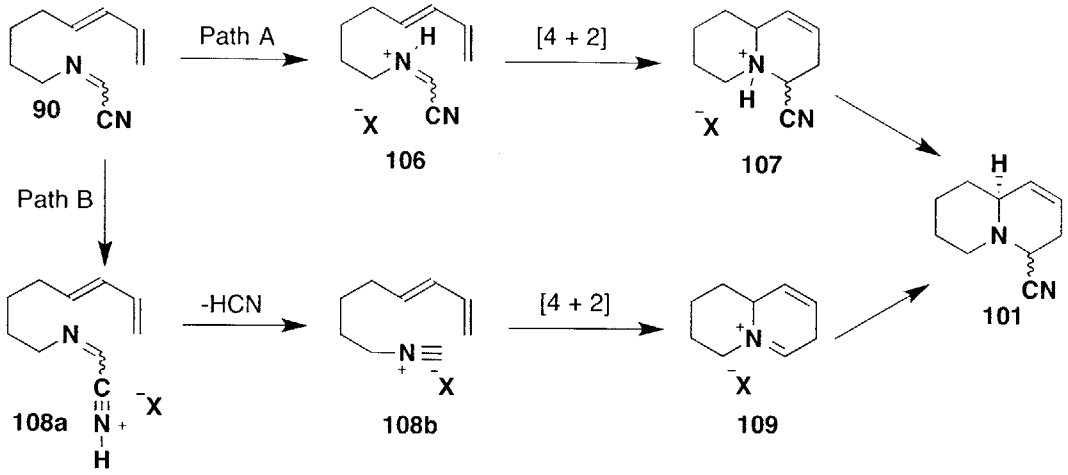
Acid-Promoted [4 + 2] Cycloadditions

The thermal cycloadditions of iminoacetonitriles afford substrates in moderate to high yields; however, there are some iminoacetonitriles that exhibit poor reactivity under thermal conditions. In our laboratory, Kevin Maloney investigated acid-promoted cycloadditions of iminoacetonitriles based on the hypothesis that Lewis acids would further activate the imines for participation in aza Diels-Alder reactions.[40] Initially, David Amos and later Maloney examined the ability of Lewis acids to promote the reaction since several metal ions have an affinity for imino and cyano groups. Lewis acid coordination to the nitrile, for example, could activate the imine by dissociation of cyanide leading to a reactive nitrilium ion, which could then participate in [4 + 2] cycloadditions. Maloney employed several Lewis acids without success, but in the case of $Cu(OTf)_2$ he observed ca. 40% of the desired cycloadduct. Maloney believed that in this case the reaction was actually catalyzed by trifluoromethanesulfonic acid formed by the reaction of $Cu(OTf)_2$ with traces of water. As a result, he began investigating Brønsted acid promoted [4 + 2] cycloadditions.

There are two possible mechanisms for the Brønsted acid promoted cycloadditions (Scheme 14). Pathway A involves protonation of the imine nitrogen in **90** to provide an activated iminium ion **106**, which then undergoes [4 + 2] cycloaddition to provide quinolizidine **101** after basic workup. In pathway B, protonation occurs on the nitrogen of the nitrile. Dissociation of HCN reveals a highly reactive nitrilium ion **108b**, which undergoes a [4 + 2] cycloaddition to provide the iminium ion **109**. Recombination with cyanide affords the desired cycloadduct **101**. Both mechanisms are conceivable; however, we believe pathway A is operating because we often observe a mixture of cyano epimers in the cycloadducts. If pathway B was favored, we would expect the cycloadducts to equilibrate by ionization under these

conditions and the cyano group would be in the more stable axial position after recombination (vide infra).

Scheme 14



The two cyano epimers can usually be equilibrated to one diastereomer by heating the mixture at 50 °C in acetonitrile for several hours. After equilibration, the cyano group is located in the axial position. This isomer is lower in energy due to an anomeric effect where the lone pair on the nitrogen donates into the σ* orbital of the C-CN bond (Figure 3). Generally, we heat the mixture of epimeric cycloadducts in a polar solvent to equilibrate them in order to facilitate structure assignments and to aid in purification, but in preparative work there is no need for this step since this stereocenter is destroyed during subsequent synthetic elaboration.

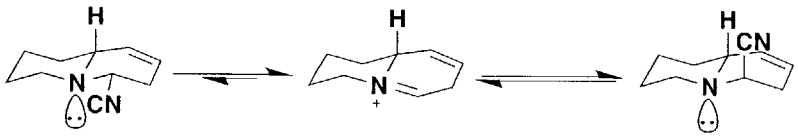
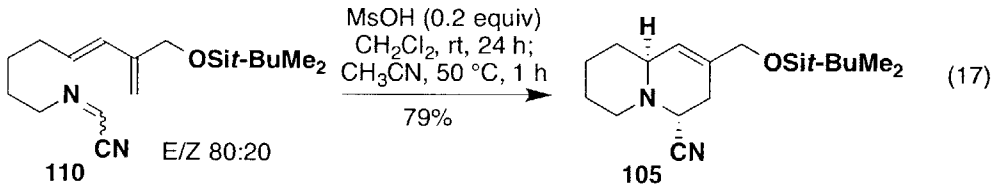


Figure 3

Maloney discovered that acids with pKa values less than -1 are effective promoters of the cycloaddition.[40] Reactions with weaker acids such as TFA and AcOH resulted in decomposition of the iminoacetonitriles by acid-promoted hydrolysis or nucleophilic addition. After extensive

screening of acids and solvents, Maloney determined that methanesulfonic acid (MsOH) in CH_2Cl_2 was the best choice for successful cycloadditions of iminoacetonitriles. The reaction also requires anhydrous conditions to prevent hydrolysis of the imine, so 4 Å molecular sieves are added to the reaction mixture as a precautionary measure.

Later, Shaun Fontaine discovered that in our cycloadditions molecular sieves react with strong Brønsted acids in an irreversible process,[43,44] so the amount of molecular sieves needs to be controlled. The cycloadditions do occur in good yield without the use of molecular sieves, but rigorous drying of reagents and solvents is necessary. In cycloadditions employing catalytic amounts of acid, drying all reagents and solvents is essential since the addition of molecular sieves destroys the acid at a competitive rate. For more reactive substrates such as **110**, Fontaine showed that a catalytic amount of MsOH is sufficient without the addition of molecular sieves (eq 17).[43]



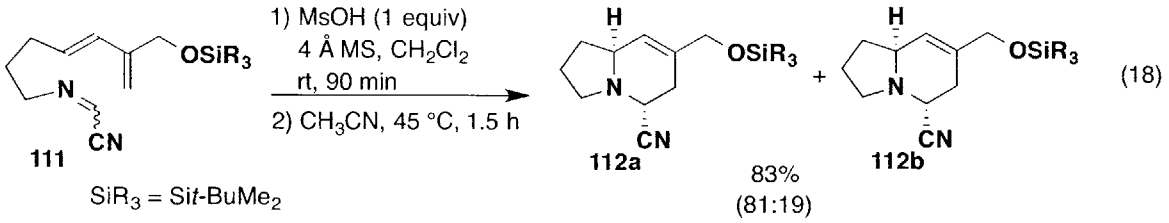
(17)

The synthesis of quinolizidines proved to be successful under both thermal and acid promoted conditions. Kevin Maloney then tried applying the acid-promoted cycloaddition conditions to a substrate with a 3-carbon tether so as to generate an indolizidine core.[40] The acid-promoted cycloaddition of iminoacetonitrile **111** provided an 81:19 mixture of cycloadducts **112a** and **112b** in 83% yield after equilibration. Indolizidine **112a** is the thermodynamic product where the nitrile is in the energetically more favorable axial position. Unlike the quinolizidine

[43] For details, see: Fontaine, S. D. Enantioselective [4 + 2] Cycloadditions of Iminoacetonitriles. Application to the Total Synthesis of (-)-Quinolizidine 207I. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2011.

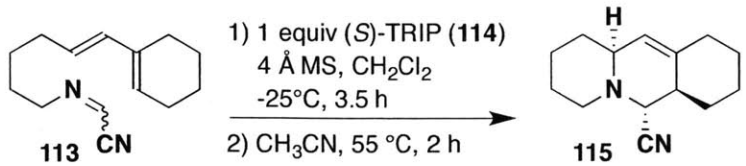
[44] For examples of molecular sieves reacting with acids, see: (a) Roelofsen, D. P.; Van Bekkum, H. *Synthesis* **1972**, 419-420. (b) Roelofsen, D. P.; Wils, E. R. J.; Van Bekkum, H. *Chem. Rec. Trav.* **1971**, *90*, 1141-1125.

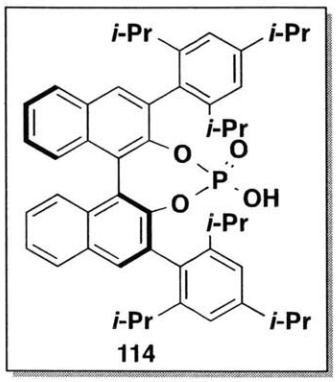
substrates, indolizidines do not equilibrate to form one epimer after heating in acetonitrile for a few hours.



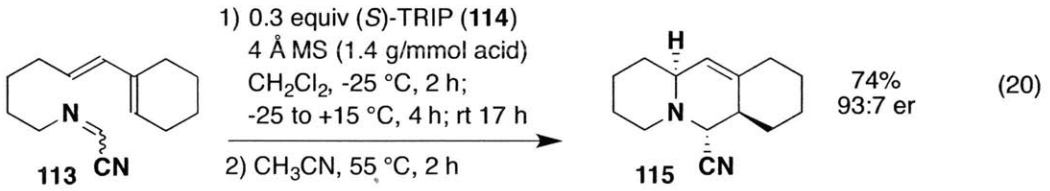
Following the success of acid promoted cycloadditions with methanesulfonic acid, Fontaine began investigating an enantioselective variant of this method, which is important for the synthesis of some natural products.[43] Previously, several research groups demonstrated the use of BINOL phosphoric acids as catalysts in aza Diels-Alder reactions.[45] However, the reactions accomplished by Fontaine represent the first aza Diels-Alder reactions of unactivated dienes with imino dienophiles promoted by BINOL phosphoric acids. Eq 19 shows one example of an enantioselective cycloaddition, which yields a tricyclic α-amino nitrile. Iminoacetonitrile **113** in the presence of 1 equiv of (*S*)-TRIP (**114**) at -25 °C undergoes a [4 + 2] cycloaddition to afford **115** in 88% yield and 93:7 enantiomeric ratio. Equilibration of the cyano epimers in warm acetonitrile is only performed to facilitate analysis of the products. Many chiral phosphoric acids were screened, but reaction with TRIP at -25 °C provides cycloadducts with the highest yield and enantiomeric ratio. One equivalent of TRIP is used in most cases to promote the cycloaddition; however, Fontaine was able to recover 90-98% of the acid. Not all substrates are produced with such high enantioselectivity, but this acid is currently the state of the art for enantioselective intramolecular aza Diels-Alder reactions with unactivated dienes.

[45] (a) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796-4798. (b) Rueping, M.; Azap, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7832-7835. (c) Liu, H.; Cun, L-F.; Mi, A-Q.; Jiang, Y-Z.; Gong, L-Z. *Org. Lett.* **2006**, *8*, 6023-6026.



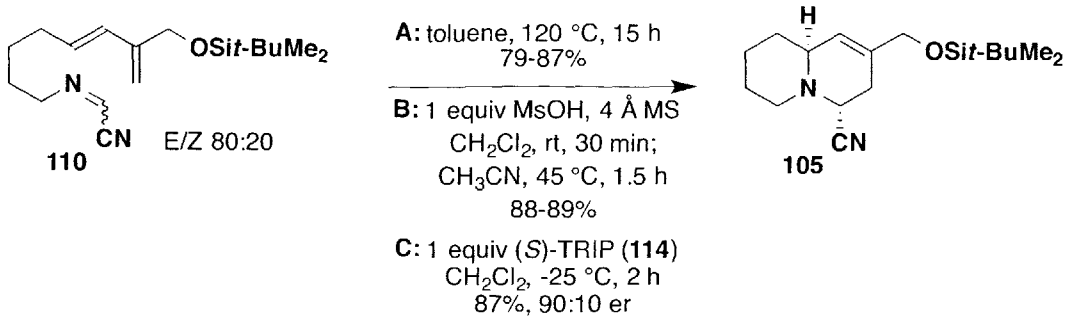


The catalytic cycloaddition of **113** was also investigated using (*S*)-TRIP to afford **115** in 74% yield with the same enantiomeric ratio as when using the stoichiometric protocol (eq 20).



In summary, the [4 + 2] cycloaddition of iminoacetonitriles works well under both thermal and Brønsted acid promoted conditions as illustrated in Scheme 15. The resulting α-amino nitriles are excellent synthetic handles for the elaboration of the cycloadducts, and examples of these transformations are outlined in the next section.

Scheme 15



The Synthetic Utility of α-Amino Nitriles

Six-membered nitrogen containing heterocycles such as quinolizidines, indolizidines, and piperidines appear in many natural products and pharmaceutical agents. Many of these important compounds contain a variety of substituents adjacent to the nitrogen. One of our primary reasons for exploring the [4 + 2] cycloadditions of iminoacetonitriles was the ability to access α-amino nitrile cycloadducts that constitute latent iminium ions for further synthetic elaboration. The chemistry of α-amino nitriles has been previously utilized in the laboratories of Polniaszek[46] and Husson, among others.[47,48]

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[46] (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688-4693. (b) Polniaszek, R. P.; Dillard, L. W. *Tetrahedron Lett.* **1990**, *31*, 797-800. (c) Polniaszek, R. P.; Belmont, S. E.; Alvarex, R. *J. Org. Chem.* **1990**, *55*, 215-225. (d) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868-4874.

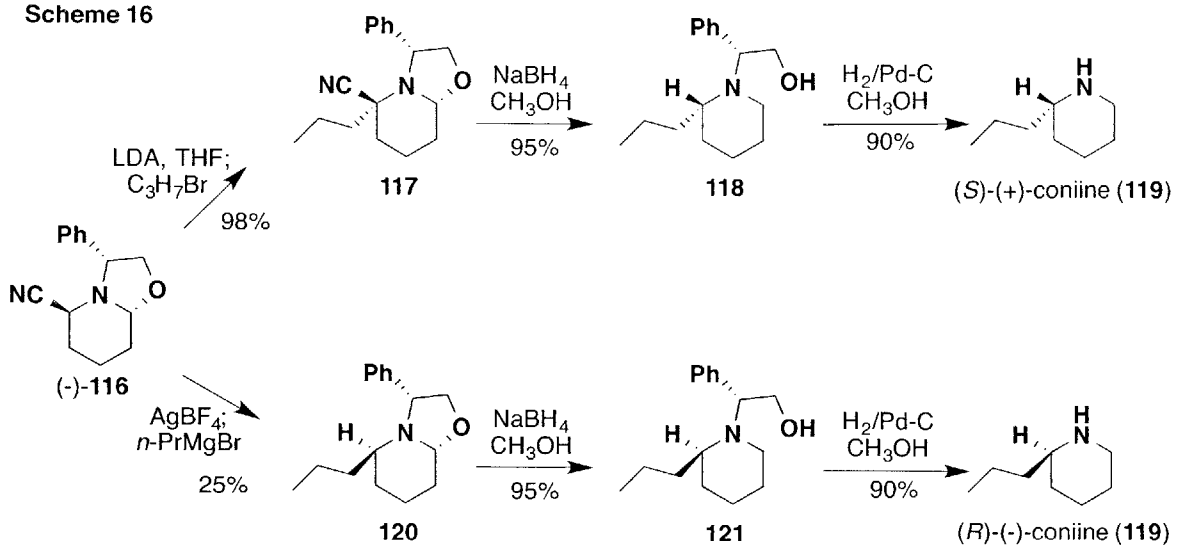
[47] For reviews on the chemistry of α-amino nitriles see: (a) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148-162. (b) Husson, H-P.; Royer, J. Chemistry of Potential and Reversed Iminium System In *Advances in the Use of Synthons in Organic Chemistry*, Dondoni, A. Ed.; Jai Press Inc.: Greenwich, CT, 1995; Vol. 2, 1-68. (c) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. (d) Husson, H-P.; Royer, J. *J. Chem. Soc. Rev.* **1999**, *28*, 383-394. (e) Enders, D.; Schilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359-373. (f) Opatz, T. *Synthesis* **2009**, 1941-1959.

[48] For several examples of the chemistry of α-amino nitriles, see: (a) Strecker, A. *Liebigs. Ann. Chem.* **1850**, *75*, 27-45. (b) Malassene, R.; Toupet, L.; Hurvois, J-P.; Moinet, C. *Synlett* **2002**, *6*, 895-898. (c) Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745-2748. (d) Wolckenhauer, S. A.; Rychnovsky, S. D. *Tetrahedron* **2005**, *61*, 3371-3381. (e) Bahde, R. J.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4017-4020. (f) Yue, C.; Royer, J.; Husson, H-P. *J. Org. Chem.* **1992**, *57*, 4211-4214. (g) Xiao, D.; Wang, C.; Palani, A.; Reichard, G.; Aslanian, R.; Shih, N-Y.; Buevich, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2596-2598. (h) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222-3231.

In 1983, Husson and coworkers demonstrated the utility of α-amino nitriles in the enantiodivergent synthesis of (*S*)-(+)-coniine and (*R*)-(-)-coniine.[49] The use of chiral α-amino nitriles for the asymmetric synthesis of natural products is defined by Husson as the CN(R,S) method.[50] Scheme 16 shows an application of the CN(R,S) method[51] for the synthesis of coniine via a stereoelectronically controlled nucleophilic attack of iminium ions, generated from α-amino nitriles. The importance of this chemistry is that one α-amino nitrile can be transformed into two products with opposite absolute stereochemistry in high stereoselectivity. Alkylation of **116** via deprotonation with LDA and reaction with *n*-propyl bromide installs a propyl group alpha to the nitrogen. Reductive decyanation and removal of the chiral auxiliary via hydrogenolysis affords (*S*)-(+)-coniine (**119**). Compound **116** can also afford the enantiomer (*R*)-(-)-coniine in the same number of steps. Instead of installing the *n*-propyl group by alkylation, treatment of **116** with $AgBF_4$ reveals a chiral iminium ion that can be trapped with *n*-PrMgBr to provide **120** as a single diastereomer. Removal of the chiral auxiliary renders (*R*)-(-)-coniine (**119**). This method, studied extensively by Husson and coworkers, shows the advantages of α-amino nitriles in organic synthesis.

[49] Guerrier, L.; Royer, J.; Grierso, D. S.; Husson, H-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754-7755.
[50] Aiken, D. J.; Royer, J.; Husson, H-P. *J. Org. Chem.* **1999**, *55*, 2814-2820.
[51] For a review of the CN(R,S) method, see: Husson, H-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383-394.

Scheme 16



The α-amino nitrile cycloadducts prepared in our laboratory allow us to access highly substituted ring systems in an efficient manner. Our laboratory has developed stereoselective methods for the elaboration of the cycloadducts prepared in the previous section. Many of the transformations proceed through an iminium ion, which is revealed when the α-amino nitrile is exposed to a Brønsted or Lewis acid. Following cyanide dissociation, the resulting iminium ion can react with nucleophiles to form new C-C or C-H bonds. The nucleophile attacks the iminium ion antiperiplanar to the developing lone pair on the nitrogen, and depending on the substrate, the facial selectivity can be very high (Figure 4).

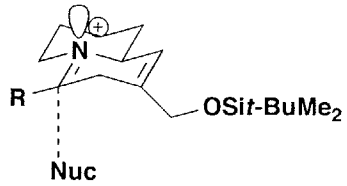
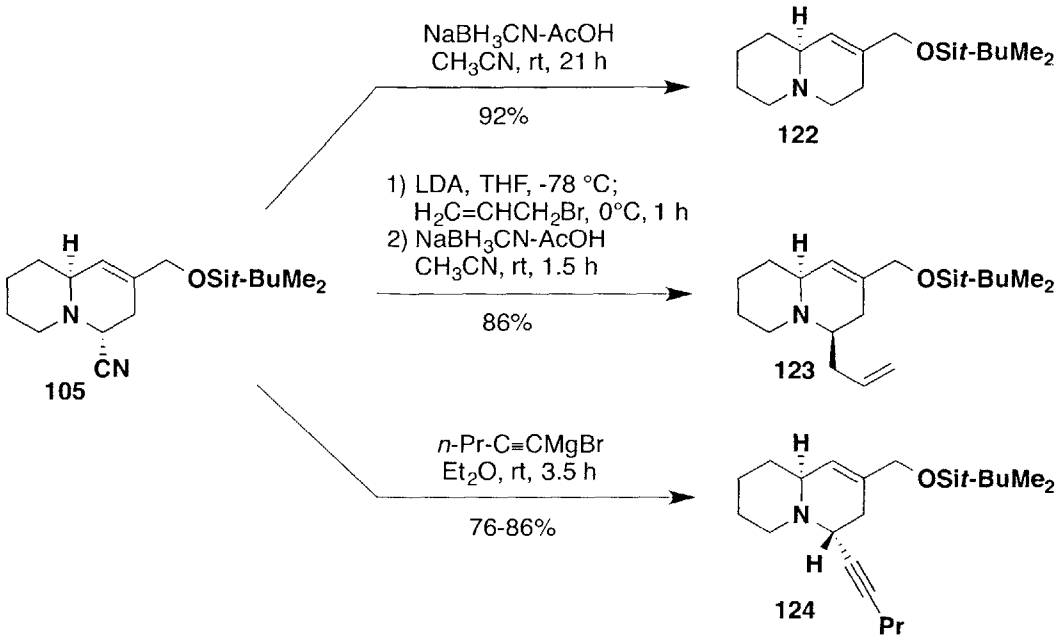


Figure 4

David Amos[39] and Kevin Maloney[40] reported several transformations of quinolizidine cycloadducts, and a few examples are shown in Scheme 17. David Amos optimized the

reductive decyanation[52] method for quinolizidine substrates by using a mixture of $NaBH_3CN$-AcOH to afford quinolizidines with no additional substitution alpha to the nitrogen as in **122**. Reductive decyanation using $NaBH_4$ in ethanol at rt also afforded **122**, but somewhat lower yield (83-85%).

Scheme 17



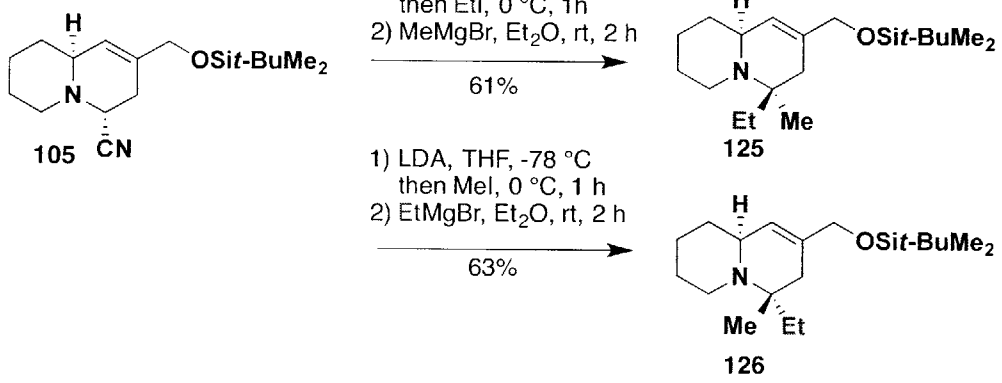
When the nucleophile is a Grignard reagent, a new carbon-carbon bond is formed, generating products such as **124**. This transformation is called a Bruylants reaction[53] and is a widely used reaction of α-amino nitriles.[54] The Mg^{2+} species, present in the Grignard reagent solution, are strong enough Lewis acids to generate the necessary iminium ion. If the target of interest has stereochemistry opposite to that of **124** there is another method that can be used to install the group adjacent to the nitrogen. An alkylation/reductive decyanation sequence

[52] For a review on reductive decyanation reactions, see: Mattalia, J-M.; Marchi-Delapierre, C.; Hazimeh, H.; Chanon, M. *ARKIVOC*, **2006**, *4*, 90-118.
[53] Bruylants, P. *Bull. Soc. Chem. Belg.* **1924**, *33*, 467.
[54] For select examples of the Bruylants reaction, see: (a) Reddy, P. V.; Smith, J.; Kamath, A.; Jamet, H.; Veyron, A.; Koos, P.; Philouze, C.; Greene, A. E.; Delair, P. *J. Org. Chem.* **2013**, *78*, 4840-4849. (b) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222-3231. (c) Beaufort-Droal, V.; Pereira, E.; Théry, V.; Aitken, D. J. *Tetrahedron* **2006**, *62*, 11948-11954. (d) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085-2088.

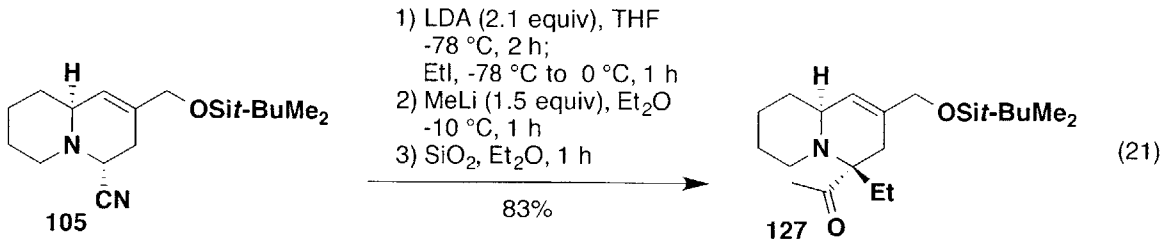
achieves this goal. For example, metalation of **105** with LDA followed by the addition of an electrophile forms an intermediate alkylated α-amino nitrile. Reductive decyanation using $NaBH_3CN$-AcOH furnishes products such as **123** where the R-group is oriented opposite to that in the product of a Bruylants reaction.

Amos combined two of the methods described above to generate quaternary centers adjacent to the nitrogen. Initially, alkylation of the α-amino nitrile cycloadduct with LDA and an electrophile provides the intermediate alkylated ring. A Bruylants reaction of this intermediate can be used to incorporate another carbon substituent alpha to the nitrogen. Depending on the electrophile and Grignard reagent used in steps one and two, the quaternary center stereochemistry can be reversed as shown in Scheme 18.

Scheme 18



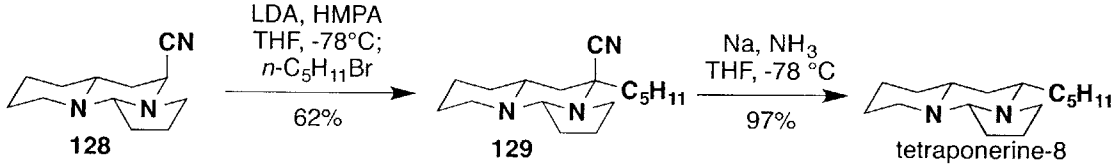
Another important class of carbon nucleophiles are alkyllithium reagents. These reagents cannot replace Grignard reagents for Bruylants reactions with α-amino nitriles. However, Amos showed that after alkylation with ethyl iodide, slow addition of methyllithium to the α-amino nitrile leads to a 1,2-addition to the nitrile to afford an imine. Upon stirring over silica gel, the imine is hydrolyzed to the corresponding ketone (**127**) in 83% yield (eq 21).



(21)

Another method commonly used for reductive decyanation of α-amino nitriles does not proceed via an iminium ion. Instead, the reductive decyanation proceeds via a radical mechanism under dissolving metal conditions.[52,55] This procedure was used by Husson in the synthesis of tetraponerine-8 (Scheme 19).[56] The dissolving metal reductive decyanation can be employed when an iminium ion cannot be generated or when there are acid sensitive functional groups present in the molecule.

Scheme 19



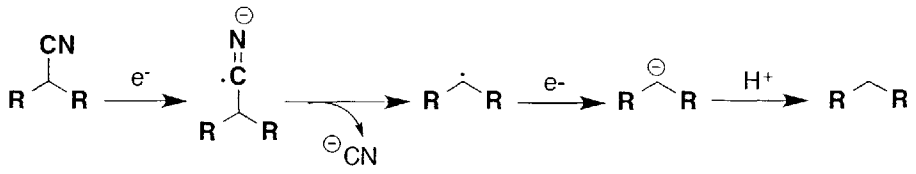
The mechanism of the dissolving metal reductive decyanation is shown in Scheme 20. In the first step a single electron adds to the nitrile. Then the carbon-carbon bond cleaves homolytically to generate a carbon-centered radical followed by an addition of another electron to form a carbanion. Protonation of the carbanion by aqueous workup or addition of an alcohol provides the decyanated product.

---

[55] For selected example of dissolving metal reductive decyanations, see: (a) Arapakos, R. G. *J. Am. Chem. Soc.* **1967**, *89*, 6794-6796. (b) Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, *1*, 61-64. (c) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H-P. *Tetrahedron Lett.* **1982**, *23*, 3369-3372. (d) Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H-P. *Tetrahedron*, **1988**, *44*, 2457-2470. (e) Nagasaka, T.; Hayashi, H.; Kumakawa, M.; Sakamoto, M.; Mizuno, M.; Hamaguchi, F. *Heterocycles* **1989**, *29*, 2157-2166. (f) Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375-8384. (g) Buckmelter, A. J.; Kim, A. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386-9390.

[56] (a) Yue, C.; Royer, J.; Husson, H-P. *J. Org. Chem.* **1990**, *55*, 1140-1141. (b) Yue, C.; Gauthier, I.; Royer, J.; Husson, H-P. *J. Org. Chem.* **1996**, *61*, 4949-4954.

Scheme 20



Summary

In summary, iminoacetonitriles are an important class of activated dienophiles that participate in aza Diels-Alder reactions. Our laboratory has developed two reliable and efficient methods for the generation of these imines, and investigated their high reactivity in [4 + 2] cycloadditions with unactivated acyclic dienes. The resulting cycloadducts participate in typical transformations of α-amino nitriles with a high degree of stereoselectivity. In the following sections, I describe recent advances in the intermolecular variant of this method, and also the application of the enantioselective [4 + 2] cycloaddition in the total syntheses of two indolizidine natural products.

Part II

Intermolecular Aza Diels-Alder Reactions of Iminoacetonitriles: A [4 + 2] Cycloaddition Route to Substituted Tetrahydropyridines

Chapter 1

Intermolecular [4 + 2] Cycloadditions of Iminoacetonitriles

Piperidines are one of the most common structures found in natural products and pharmaceuticals, appearing in over 12,000 compounds in clinical and preclinical studies between 1988 and 1998.[57] The important biological properties of these compounds have motivated many research groups to develop efficient routes for the synthesis of piperidines.

Previously, piperidines have been synthesized by a variety of methods including ring closing metathesis, by cyclizations via reductive amination and nucleophilic substitution, and by reduction of pyridines.[58] However, the aza Diels-Alder reaction utilizing imino dienophiles is one of the most valuable approaches to these six-membered heterocycles.[4d] Although many classes of imines participate in [4 + 2] cycloadditions (see Part I, Chapter 1), Bailey and coworkers have reported the type of imines that are presently the state of the art for reactions with acyclic *unactivated* dienes. The cycloaddition between Bailey's benzhydryl imine **33** and a variety of simple acyclic dienes proceeds in moderate to high yield as shown in eq 22. The most significant limitation of this method is that many natural product targets have 2,6-*trans* substituents on the piperidine ring. Although, the method reported by Bailey proceeds with high diastereoselectivity, it only provides direct access to 2,6-*cis* systems. Another limitation of this method is the constraints based on the structure of the dienophile. The ester substituent present

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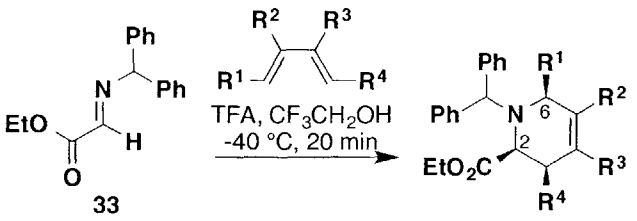
[57] Watson performed a substructure search of the piperidine ring in Drug Data Report (MDL Drug Data Report). See, Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679-3681.

[58] For reviews on the chemistry and synthesis of piperidines, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633-639. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781-1913. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953-2989. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701-1729. (e) Felpin, F-X.; Lebreton, J. *Curr. Org. Synth.* **2004**, *1*, 83-109. (f) Girling, P. R.; Kiyoi, T.; Whiting, A. *Org. Biomol. Chem.* **2011**, *9*, 3105-3121.

in the cycloadduct is not easily cleaved or converted to other substituents, limiting the range of targets directly available using this method.



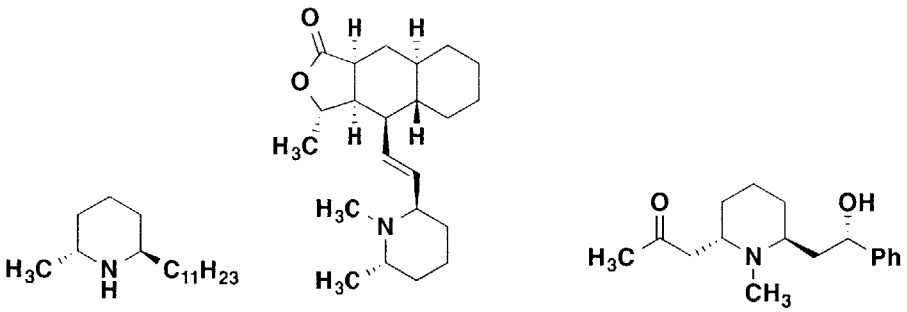
34	R^1, R^4 = H; R^2 R^3 = CH_3	95%
35	R^1, R^2, R^4 = H; R^3 = CH_3	87%
36	R^2, R^3 = H; R^1, R^4 = CH_3	60%
37	R^2, R^3, R^4 = H; R^1 = CH_3	62%
38	R^3, R^4 = H; R^1, R^2 = CH_3	42%

(22)

An efficient synthesis of *trans*-2,6-piperidines is important because of the number of biologically active compounds that contain these structures. Scheme 21 depicts a few members of this class of heterocycles found in nature. (-)-Solenopsin A (**130**) is found in the venom of the Solenopsis species of fire ants.[59] (+)-Himbacine (**131**) was isolated from the bark of *Galbulimina baccata*, from the Magnolia family.[60] Both solenopsin A and himbacine are drug candidates for the treatment of Alzheimer's disease.[61] Another piperidine natural product is (-)-sedacrine[62] (**132**), a toxic piperidine isolated from the horsetail plant *Equisetum paluster* L. in Europe. Although the bioactivity of this natural product is not known, sedacrine belongs to a large class of alkaloids that have recently become of interest in neurological disorder studies. A common feature of these three natural products is the *trans* relationship between the substituents at C2 and C6.

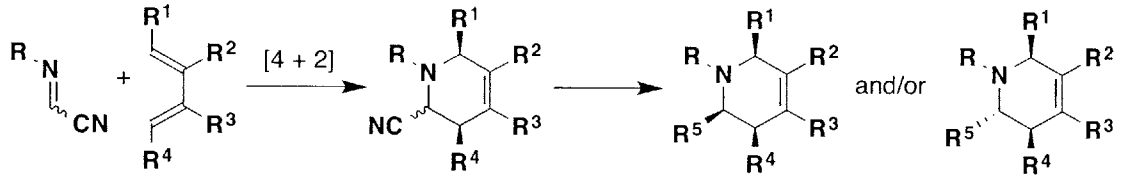
[59] Jones, T. H.; Blum, M. S. *Tetrahedron* **1982**, *38*, 1949-1958.
[60] For the isolation of himbacine, see: Brown, R. F. C.; Drummond, R.; Fogerty, A. C.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1956**, *9*, 283-287.
[61] Takadoi, M.; Yamaguchi, K.; Terashima, S. *Bioorg. Med. Chem.* **2003**, *11*, 1169-1186.
[62] For synthesis of sedum alkaloids see: Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957-5978.

Scheme 21



The importance of piperidines as molecules of interest to the pharmaceutical industry inspired our laboratory to explore intermolecular [4 + 2] cycloadditions of iminoacetonitriles. Previously we demonstrated the utility of this new class of dienophiles in *intramolecular* [4 + 2] cycloadditions with a wide selection of unactivated dienes (Part I, Chapter 2). Kevin Maloney carried out some initial studies on the development of the *intermolecular* reaction with the aim to not only perform cycloadditions with iminoacetonitriles, but also to elaborate the α-amino nitrile cycloadducts to produce *both* 2,6-*cis* and 2,6-*trans* piperidines with high stereoselectivity (Scheme 22).

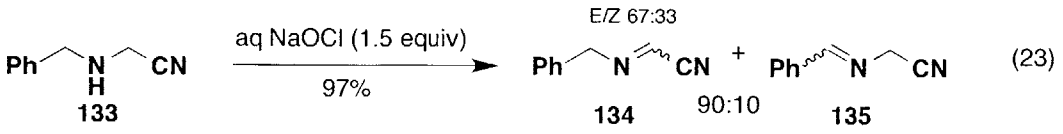
Scheme 22



Iminoacetonitrile Synthesis

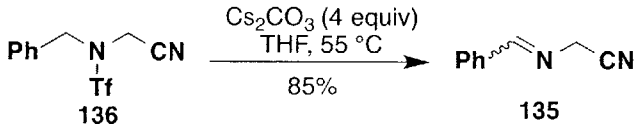
Maloney's[40] studies focused on *N*-benzyliminoacetonitrile as the dienophile because of the possibility to remove the benzyl group at a later stage in the piperidine synthesis. Selva previously synthesized *N*-benzyliminoacetonitrile from *N*-benzylaminoacetonitrile and NaOCl.[37]

Chlorination of the secondary amine **133** with NaOCl followed by elimination of HCl in a one-pot process furnished a 90:10 mixture of **134** and **135** in 97% yield. Imine **135** is a common byproduct of this reaction due to the stability of the imine in which the π-bond is in conjugation with the aromatic ring. Maloney had difficulty in separating the two imines, so a new synthesis of *N*-benzyliminoacetonitrile **134** became necessary.



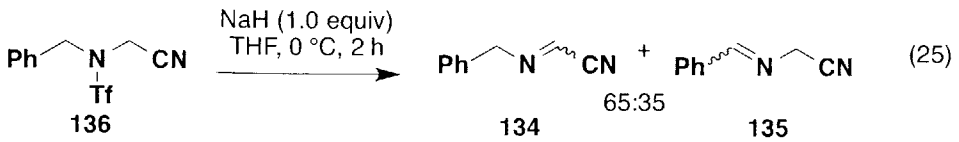
(23)

Initially, Dave Amos attempted to use the Mitsunobu approach to synthesize iminoacetonitrile **134** since that method had proved very successful in generating the substrate for intramolecular iminoacetonitrile cycloadditions. The Mitsunobu reaction between benzyl alcohol and the Amos reagent ($TfNHCH_2CN$) afforded **136** in 85% yield. Unfortunately, warming triflamide **136** in the presence of Cs_2CO_3 resulted in undesired imine **135** in high yield and none of the desired imine.



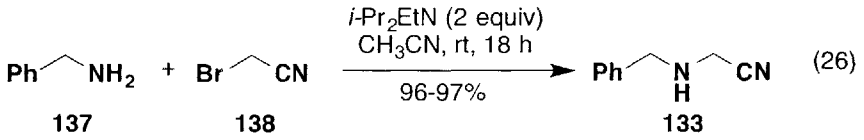
(24)

Amos tried other bases and lower temperatures for the elimination but had little success. Stirring triflamide **136** at 0 °C in the presence of NaH afforded the desired iminoacetonitrile contaminated with ca. 35% of *C*-phenyl imine **135** (eq 25). After screening different conditions for the elimination of trifluoromethanesulfinate, Maloney decided to explore an alternate method for the synthesis of **134**.

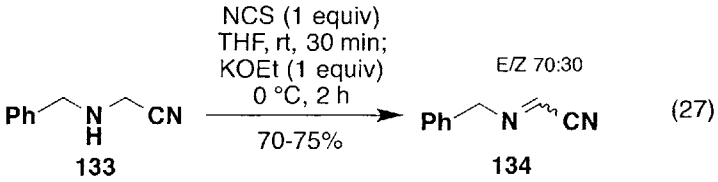


(25)

Instead of proceeding via the triflamide, Maloney examined routes based on the corresponding *N*-chloro amine. Alkylation of phenylamine with bromoacetonitrile following a known procedure[63] furnished *N*-phenylaminoacetonitrile in excellent yield (eq 26). With the α-amino nitrile in hand, the next goal was to effect elimination to the imine without the formation of isomeric imine **135**. Maloney reported that he was able to isolate **134** in 70-75% yield as a 70:30 mixture of E/Z iminoacetonitriles under the conditions shown in eq 27. Thus, chlorination of **133** with *N*-chlorosuccinimide followed by the addition of KOEt at 0 °C afforded iminoacetonitrile **134** with less than 1% of the undesired imine.



(26)



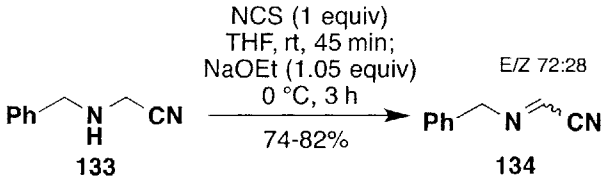
(27)

This was an excellent improvement over the method reported by Selva for the synthesis of *N*-benzyliminoacetonitrile. Unfortunately, the result was difficult to reproduce. When I began exploring this chemistry, I observed two different outcomes of this reaction. In some cases, when I added 1 equivalent of KOEt, I observed incomplete elimination and isolated *N*-chloro amine after column chromatography. In other cases, I observed the undesired *C*-phenyl imine (**135**). Addition of 1.3 equivalents of KOEt to the reaction mixture resulted in further isomerization to the undesired imine. Concerned that the purity of commercial KOEt was affecting the reaction, I also prepared KOEt from potassium metal and ethanol. Employing both

[63] For a detailed procedure for the related reaction of 1-phenylethylamine with bromoacetonitrile, see: Tokuyama, H.; Kuboyama, T.; Fukuyama, T. *Org. Synth.* **2003**, *80*, 207-212.

KOEt prepared in the laboratory and commercial reagent, either unreacted *N*-chloro amine was observed or isomerization to the undesired imine isomer occurred.

We then turned our attention to using sodium ethoxide as the base because it can be easily generated at a known concentration from the reaction of sodium metal and ethanol. Reaction of exactly 1 equivalent of this base with freshly prepared *N*-chloro amine at 0 °C for 3 h effected the desired elimination without isomerization of the imine. Only ca. 3% of unreacted *N*-chloro amine was isolated under these conditions. Adding a slight excess of base (1.05 equiv) resulted in pure iminoacetonitrile in 74-82% yield as a 72:28 mixture of E/Z imines (eq 28). This optimized method for the synthesis of *N*-benzyliminoacetonitrile **134** has proven to be both efficient and reliable.[64]



(28)

Iminoacetonitrile **134** isomerizes on silica gel to the undesired imine so it is important to purify the imine on acetone-deactivated silica gel immediately following workup. As a solution in dichloromethane, imine **134** is relatively stable at room temperature for short periods of time, but slowly decomposes and requires repurification. However, at -20 °C in a dilute degassed solution in CH_2Cl_2, the imine is stable for several months before any isomerization is observed.

Diene Synthesis

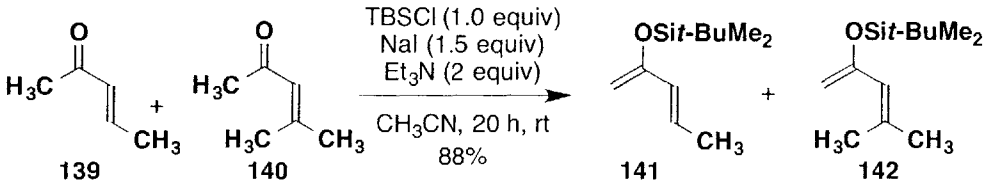
Many of the dienes used in our intermolecular cycloaddition studies are commercially available (i.e., isoprene, cyclohexadiene, 2,6-hexadiene, etc.). Other dienes of interest required a

[64] Another member of our laboratory, Linh Bui, has used this protocol to synthesize *para*-methoxybenzyliminoacetonitrile on a 4.5 g scale in 73% yield.

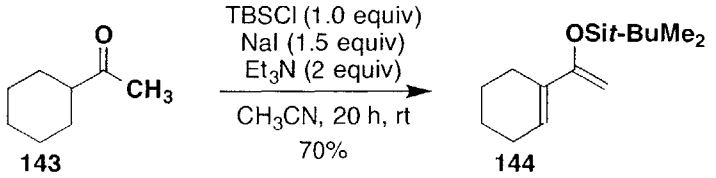
short synthesis. Two classes of dienes of particular interest to us included 2-(*tert*-butyldimethylsilyloxy)-substituted dienes and thio-substituted dienes.

2-(tert-Butyldimethylsilyloxy) Dienes

We became interested in this class of dienes because not only are they readily available from the parent enones, but the silyloxy group can act as a regiochemical directing group to afford cycloadducts with interesting substitution patterns in high selectivity. Several 2-(*tert*-butyldimethylsilyloxy) butadiene derivatives were synthesized from the corresponding ketones and are shown below. Diene **141**[6566] was synthesized as shown in eq 29 but was obtained as a 90:10 mixture of isomers. The contaminant diene **142** does not participate in the aza Diels-Alder reaction so it is not necessary to separate it from the desired diene. Diene **144**[67] was synthesized in 70% yield following the same procedure (eq 30). These dienes were purified by column chromatography on acetone-deactivated silica gel. Silica gel deactivation is required or hydrolysis of the dienes occurs.



(29)



(30)

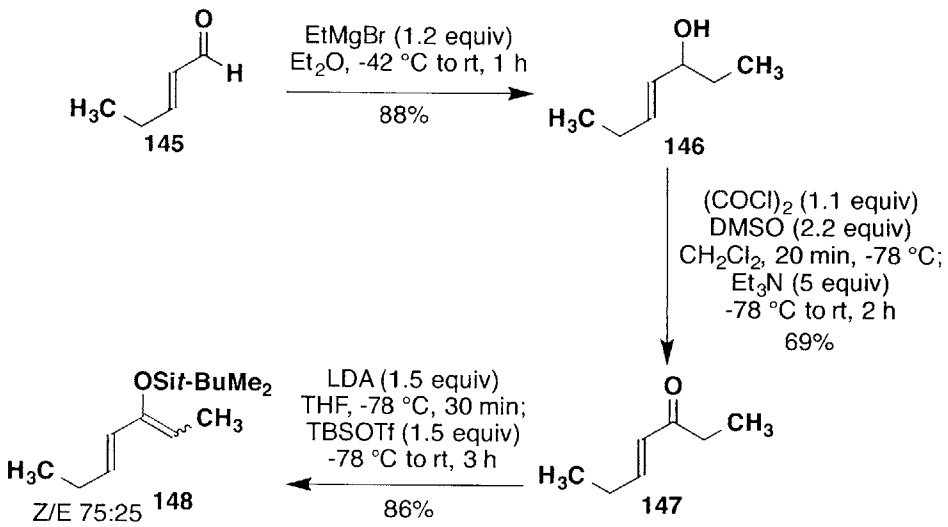
[65] (a) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529-3530. (b) Liu, H-J.; Wang, D-X.; Kim, J. B.; Browne, E. N. C.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 899-912. (c) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485-2490.

[66] Enone **139** was commercially available in technical grade containing mesityl oxide.

[67] For an alternate route to diene **144**, see: Jung, M. E.; Nishimura, N. *Org. Lett.* **2001**, *3*, 2113-2115.

We also synthesized diene **148** in three straightforward steps from commercially available *trans*-2-pentenal. Grignard addition to aldehyde **145** afforded alcohol **146** in excellent yield.[68] Swern oxidation of alcohol **146** followed by generation of the enolate and trapping with *tert*-butyldimethylsilyl trifluoromethanesulfonate afforded the desired diene **148** as a 75:25 mixture of Z/E dienes in 86% yield.

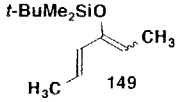
Scheme 23



NMR data for silyoxy diene **148** was compared to data reported in the literature for another silyloxy diene (**149**) prepared with using similar conditions, revealing the (E,Z)-diene is the major isomer.[69] The synthesis of silyloxy dienes from the corresponding enones using LDA or Et_3N generally forms the (E,Z)-diene as the major product (many confirmed by NOE experiments).[70] At the time, formation of the potassium enolate as reported in eq 31 was not

[68] For the synthesis of **146**, see: (a) Hayes, P. Y.; Chow, S.; Rahm, F.; Bernhardt, P. V.; De Voss, J. J.; Kitching, W. *J. Org. Chem.* **2010**, *75*, 6489-6501. (b) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718-9719.

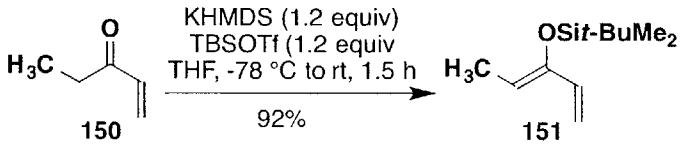
[69] Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626-9627.



[70] For examples of silyoxy diene syntheses, see: (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246-1255. (b) Friedman, S. H.; Ganapathi, P. S.; Rubin, Y.; Kenyon, G. L. *J. Med. Chem.* **1998**, *41*, 2424-2429. (c) Yamamoto, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 7082-7085.

attempted. The mixture of (E,Z) and (E,E) dienes was used without separation since only the (E,Z) isomer participates in the Diels-Alder reaction.

Diene **151** was generated from ethyl vinyl ketone in one step following a literature procedure.[71] Deprotonation of ketone **150** with KHMDS followed by enolate trapping with *tert*-butyldimethylsilyl trifluoromethanesulfonate afforded **151** in 92% yield.



150 151 (31)

Phenylthio-Substituted Dienes

Another class of dienes of interest to us as 4π components in [4 + 2] cycloadditions of iminoacetonitriles were sulfur-substituted dienes. We began studying cycloadditions of these dienes in the hope that the thiophenyl group would be a good directing group and that could be easily cleaved to give substituted piperidines with regiochemistry that would not be available by direct cycloadditions.

Sulfur substituted dienes have been studied extensively. Chou and coworkers have demonstrated the utility of 2-(phenylthio)-1,3-butadienes[72] in [4 + 2] cycloadditions with isocyanates.[73] The most common method for the synthesis of these dienes involves thermolysis

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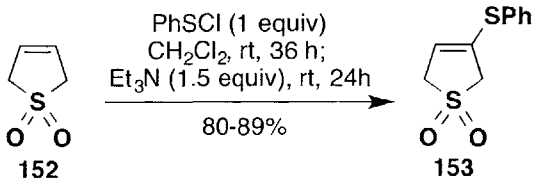
[71] For a detailed procedure for the preparation of **151**, see: Carreño, M. C.; Ruano, J. L. G.; Remor, C. Z.; Urbano, A. *Tetrahedron:Asymmetry* **2000**, *11*, 4279-4296.

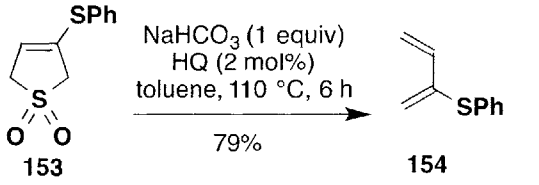
[72] For the preparation of 2-(phenylthio)-1,3-butadienes, see: (a) Gundermann, K-D.; Holtmann, P. *Angew. Chem., Int. Ed.* **1966**, *5*, 668. (b) Chou, S-S. P.; Liou, S-Y.; Tsai, C-Y.; Wang, A-J. *J. Org. Chem.* **1987**, *52*, 4468-4471. (c) Chou, T.; Lee, S-J.; Peng, M-L.; Sun, D-J.; Chou, S-S. P. *J. Org. Chem.* **1988**, *53*, 3027-3931. (d) Chou, S-S. P.; Tsao, H-J. *J. Chin. Chem. Soc.* **1993**, *40*, 53-57. (e) Bäckvall, J-E.; Ericsson, A. *J. Org. Chem.* **1994**, *59*, 5850-5851. (f) Chou, S-S. P.; Sun, D-J.; Tai, H-P. *J. Chin. Chem. Soc.* **1995**, *42*, 809-814. (g) Chou, S-S. P.; Chao, M-I. *Tetrahedron Lett.* **1995**, *36*, 8825-8828. (h) Chou, S-S. P.; Chao, M-H. *J. Chin. Chem. Soc.* **1996**, *43*, 53-59. (i) Cai, M-Z.; Wang, D.; Wang, P-P. *J. Organomet. Chem.* **2006**, *691*, 737-740.

[73] For examples of aza Diels-Alder reactions with sulfur-substituted dienes, see: (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753-786. (b) Chou, S-S. P., Yu, Y-J. *Tetrahedron Lett.* **1997**, *38*, 4803-4806 .(c) Chou, S-S. P.; Hung, C-C. *Tetrahedron Lett.* **2000**, *41*, 8323-8326. (d) Chou, S-S. P., Hung, C-C. *Synth. Commun.* **2001**, *31*, 1097-1104. (e) Chou, S-S. P.; Hung, C-C. *Synth. Commun.* **2002**, *32*, 3119-3126. (f) Chou, S-S. P.; Chen K-W. *Synth. Commun.* **2004**, *34*, 4573-4582.

of sulfolenes.[74] Following a literature procedure reported by Chou we installed the thiophenyl group in excellent yield in a one-pot procedure using commercially available **152** (eq 32).[73d] Thermolysis of **152** in the presence of hydroquinone and $NaHCO_3$ (to prevent radical and acid-promoted side reactions) afforded 2-(thiophenyl)-butadiene in good yield (eq 33).



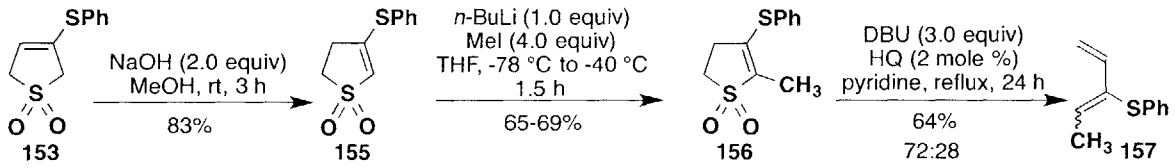
(32)



(33)

We synthesized another sulfur-substituted diene, 1-methyl-2-(phenylthio)-butadiene (**157**), following procedures reported by Chou.[75] The thermolysis of sulfolene **156** afforded **157** as a 72:28 mixture of Z/E dienes. The mixture was used without separation of the isomers since we expected only the Z isomer participates in Diels-Alder reactions.

Scheme 24



With a variety of dienes in hand, we were in a position to explore the scope of the intermolecular aza Diels-Alder reaction of iminoacetonitriles.

[74] McGregor, S. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 2858-2859.
[75] For the synthesis of **157**, see: (a) Ref. 72b,f,h. (b) Chou, S-S. P.; Hung, C-C. *Synthesis* **2001**, 2450-2462.

Intermolecular [4 + 2] Cycloadditions of Iminoacetonitriles

After synthesizing several conjugated dienes and optimizing the synthesis of *N*-benzyliminoacetonitrile, the next goal was to explore the reactivity of iminoacetonitrile **134** ($PhCH_2N{=}CHCN$) in [4 + 2] cycloadditions with a variety dienes. Maloney began studying the feasibility of the cycloaddition by testing the reactivity of iminoacetonitrile **134** under thermal conditions. Heating *N*-benzyliminoacetonitrile, isoprene, and 3 equiv of BHT in toluene at 120 °C resulted in no cycloadduct and only recovered imine. Maloney then decided to test the Brønsted acid conditions previously optimized for intramolecular cycloadditions.

Unactivated Dienes

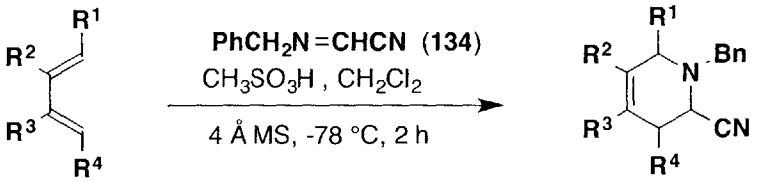
Maloney utilized four dienes[76] in this initial study of the reactivity of *N*-benzyliminoacetonitrile. He observed that 1.5 equiv of diene and 1.0 equiv of methanesulfonic acid (MsOH) were sufficient to facilitate the cycloaddition in good yields. I continued these preliminary studies and obtained the results described in the rest of this chapter with regard to optimal conditions and the scope of the intermolecular cycloaddition.

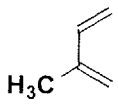
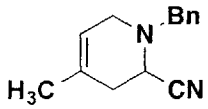
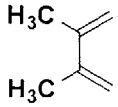
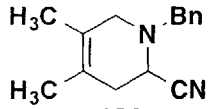
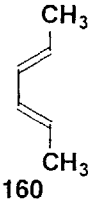
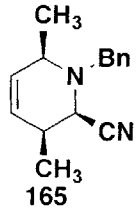
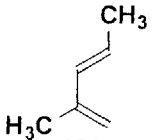
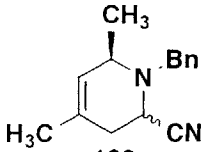
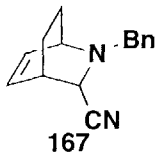
We found that in order to obtain high and reproducible yields for the cycloadditions, excess MsOH and diene are required. Table 1 shows the scope of the [4 + 2] cycloaddition reaction with several unactivated dienes. Method A employs 1.0 equiv of MsOH and 1.5 equiv of diene. In most cases method B gives the most reproducible yields. This protocol involves the use of 1.5 equiv of MsOH and 4.0 equiv of the diene. Excess diene is needed because under acidic conditions some dienes polymerize before reacting in the desired cycloaddition. We hypothesized that excess MsOH is needed because small amounts are consumed by diene

[76] Maloney examined the reactivity of isoprene, 2,4-hexadiene, 2-methyl-1,3-pentadiene, and 2-(*tert*-butyldimethylsiloxy)-1,3-pentadiene in the acid promoted [4 + 2] cycloadditions of *N*-benzyliminoacetonitrile.

polymerization, and as mentioned earlier, by reaction with the 4 Å molecular sieves that are used in our acid promoted cycloadditions as a precautionary measure to prevent imine hydrolysis under the reaction conditions.

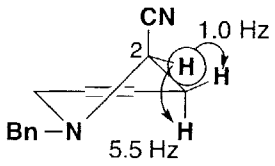
Table 1. Intermolecular [4 + 2] Cycloadditions of *N*-Benzyliminoacetonitrile with Simple Unactivated Dienes



entry	diene	cycloadduct[a]	yield (%)[b] method A	yield (%)[b] method B
1	 **158**	 **163**	-	74-85
2	 **159**	 **164**	85	95
3	 **160**	 **165**	-	71-73
4	 **161**	 **166**	-	75-77 65[c]
5	 **162**	 **167**	38-41	41

[a] Cycloadducts are isolated without equilibration of the cyano epimers. Cycloadduct **165** is the only epimer isolated after column chromatography. [b] Isolated yield of products purified by chromatography. Method A: 1.0 equiv MsOH, 1.5 equiv diene. Method B: 1.5 equiv MsOH, 4.0 equiv diene. [c] 2.8 Equiv of diene was used.

In all cases, we found the aza Diels-Alder reaction to proceed with a high degree of regioselectivity. The reaction of iminoacetonitrile **134** with isoprene at -78°C affords cycloadduct **163** in 74-85% yield as a single regioisomer. Decreasing the amount of isoprene or MsOH employed in this case does decrease the yield significantly. For example, when using 1.5 equiv of isoprene and 1.5 equiv of MsOH, **163** was isolated in 43% yield, and when using 1.5 equiv of isoprene and 1.0 equiv of MsOH yields ranged from 25-68%. Interpretation of the ^{1}H NMR spectrum of **163** provides evidence that the nitrile adopts a pseudoaxial orientation. The proton at C2 is in an equatorial position and appears in the NMR spectrum as a doublet of doublets with J-values of 5.5 Hz and 1.0 Hz. The two J-values are indicative of an axial-equatorial and an equatorial-equatorial coupling between protons.[77]



163

^{1}H NMR 3.83 ppm
dd (J = 5.5, 1.0 Hz)

Figure 5

Work performed by Husson supports our assignment of cycloadduct **163** since he previously synthesized similar α-amino nitriles and carried out extensive NMR analysis and reactions to assign their structures.[78] The structure of compound **168** was deduced based on a broad AB resonance system for the benzyl protons (3.30, 4.20 ppm, J = 14.0 Hz). The use of benzyl protons as an indicator of structure symmetry of a molecule is described in a following section (page 74). Husson also observed J-values between H2 and $H3_{eq}$ of 2.0 Hz, and a J-coupling between H2 and $H3_{ax}$ of 6.0 Hz. The assignment of the deshielded methyl group being

[77] We do not observe an axial-axial coupling for any of the cycloadducts either because the nitrile prefers to be axial or there is overlap of the two epimers in the ^{1}H NMR.
[78] Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H-P. *J. Org. Chem.* **1984**, *49*, 2392-2400.

pseudoequatorial is supported by the ^{13}C shift at 20.1 ppm.[79] The H6 proton shift is used to help facilitate our structural assignments.

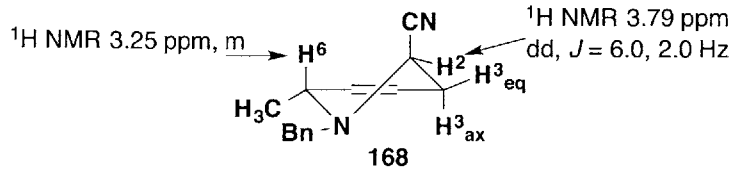
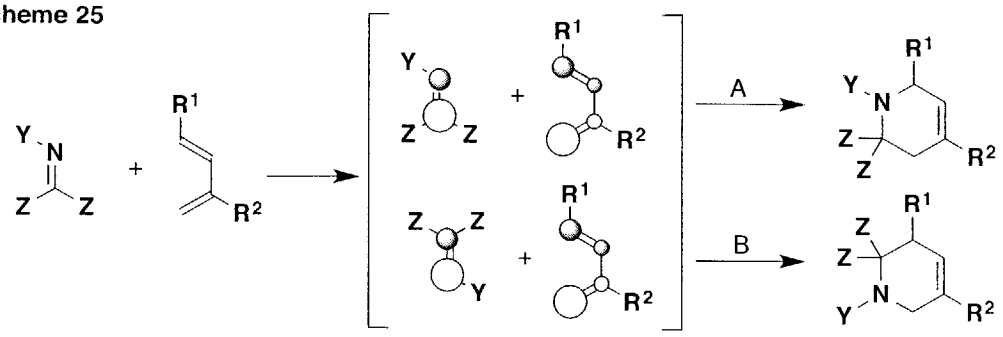


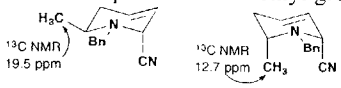
Figure 6. Husson Assignment

The regiochemical outcome of hetero Diels-Alder reactions can be predicted using frontier molecular orbital theory. Generally, the interaction of the LUMO of the dienophile and the HOMO of diene are of importance in aza Diels-Alder reactions. For butadienes containing an alkyl group at C2, the largest HOMO coefficient is at C1.[80] Most imines have a larger LUMO coefficient on the carbon and afford cycloadducts via route A in Scheme 25. However, there are examples of imines with two electron-withdrawing groups on the carbon-nitrogen double bond putting the larger LUMO coefficient on the nitrogen of the imine. In this case the cycloaddition follows pathway B to afford the other regioisomer.

Scheme 25



[79] For piperidines a pseudoaxial methyl group is often observed upfield from a pseudoequatorial methyl group.[78]



[80] For a detailed description of FMO theory, see: Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*; John Wiley & Sons: United Kingdom, 2009.

A calculation of the electron density for N-methyliminoacetonitrile was performed by Kevin Maloney using HF 6-311+G** basis set. The calculation shows that the greater electron density of the carbon-nitrogen double bond is on the nitrogen atom (Figure 7).

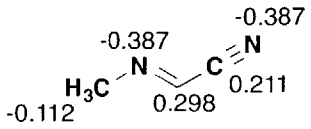
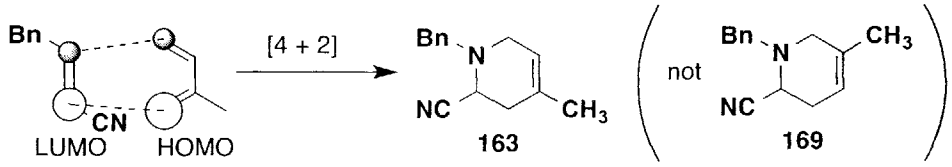


Figure 7. Electron densitiy calculation (HF 6-311+G**)

The electron density calculation is supported by our experimental results, where the larger LUMO coefficient of the iminoacetonitrile is on the carbon of carbon-nitrogen double bond and overlaps with the HOMO of isoprene to provide regioisomer **163** as shown in Scheme 26. We can use this model to help us predict the regiochemistry of the other cycloadducts.

Scheme 26



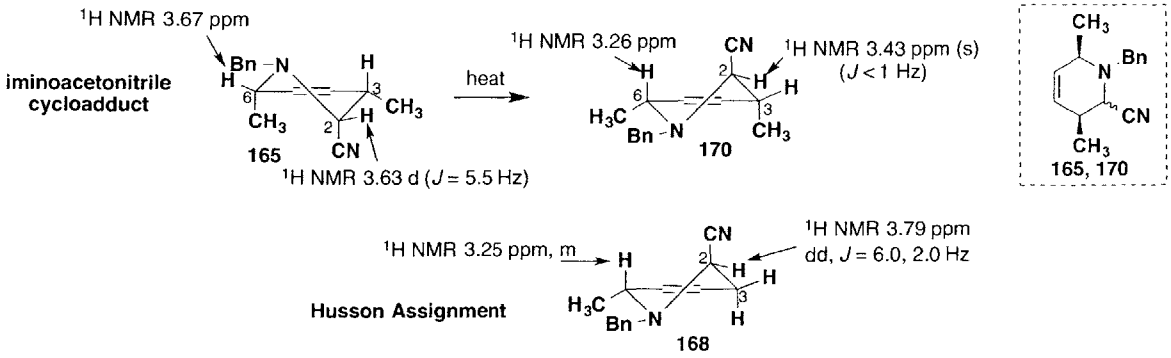
In the cycloaddition of iminoacetonitrile **134** with 2,3-dimethylbutadiene **159**, the yield of **164** was excellent using both methods A and B. Again, the yield is somewhat lower when only 1.5 equiv of diene and 1.0 equiv of MsOH are used. The J-values (6.5 and 1.0 Hz) for the proton at C2 agree with predicted values for a conformer in which the cyano group has an axial orientation.

The stereochemical course of the intermolecular cycloaddition of iminoacetonitriles was examined by reaction of the commercially available unactivated 2,6-hexadiene (**160**). The stereochemistry of cycloadduct **165**, formed in 71-73% yield, suggests that the mechanism of the cycloaddition is concerted and involves suprafacial addition rather than being a stepwise, ionic process. This is supported by the formation of the product in which the methyl groups at C3 and

C6 are cis on the new ring in **165**. The ^{1}H resonance at C6 appears at 3.67 ppm for **165**, which is representative as an equatorial proton shifted downfield from the axial H6 proton at 3.26 ppm in **170**. Maloney performed reductive decyanation of **165** to determine the favored orientation of the C3 methyl as axial without the cyano present. Further assignment of the two methyl groups is supported later in the synthesis of 2,3,6-trimethylpiperidine. The stereochemical assignment that the cyano group is cis to the two methyl groups is supported by the coupling constants shown in Scheme 27. Upon standing, the cycloadduct **165** begins to isomerize to the more stable epimer **170** as previously observed in the case of quinolizidine cycloadducts. We were able to complete the equilibration of the epimers by heating at 50 °C in acetonitrile for several hours. For these tetrahydropyridines, we only employed equilibration to facilitate structural assignments, and it should be noted that for preparative work there is no need to equilibrate the isomeric nitriles prior to further synthetic elaboration.

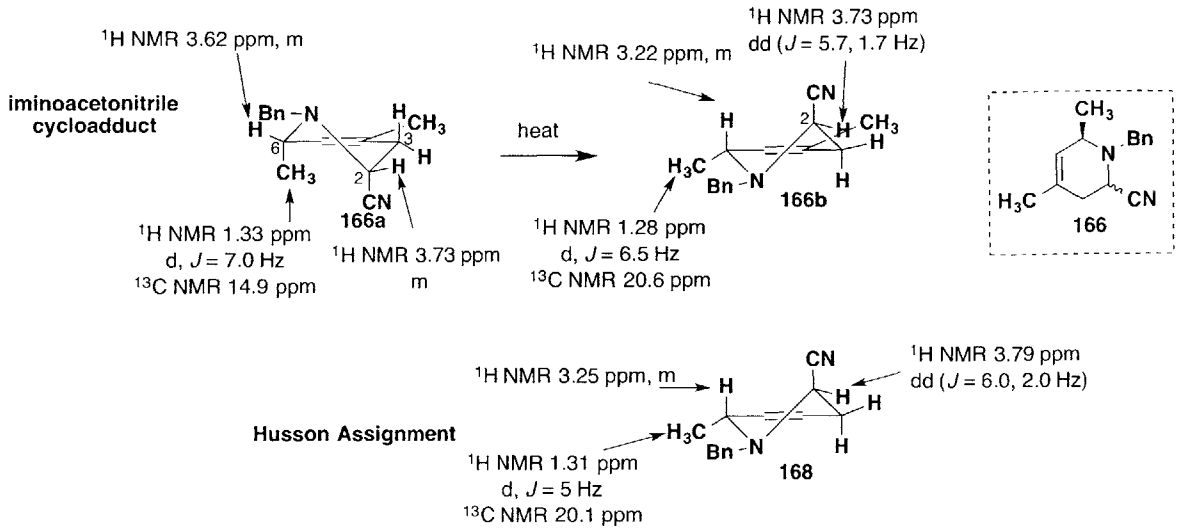
The more stable epimer **170** can be compared to a structure Husson previously assigned (**168**). We know that the methyl group at C6 is in the equatorial position because the protons at C6 in both **170** and **168** appear as multiplets with similar shifts (3.26 and 3.25 ppm respectively). With the cyano group in the axial position, the proton at C2 adopts a pseudoequatorial orientation. In our tetrahydropyridine **170**, the small equatorial-equatorial coupling leads to a singlet in the ^{1}H NMR spectrum. The coupling constant (5.5 Hz) of the proton at C2 in **165** also agrees with the equatorial-axial relationship between the protons at C2 and C3 shown in Scheme 27.

Scheme 27



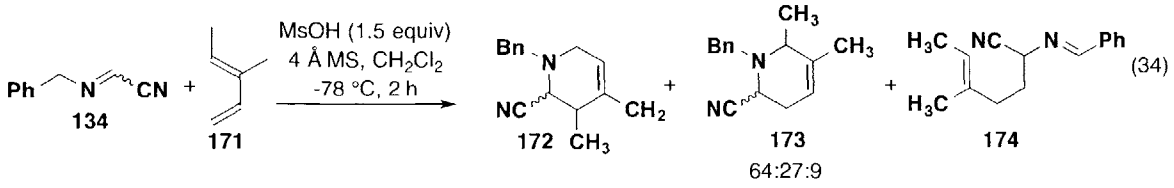
We can also use the NMR data that Husson reported to assign the structure of cycloadduct **166**, which we found forms as a 33:67 mixture of cyano epimers in 75-77% yield. From the equilibration experiment we expected that the thermodynamic product will be the 2,6-*trans* tetrahydropyridine with the nitrile in the axial position and the C6 methyl group in an equatorial orientation. The structure and stereochemical assignment of cycloadduct **166** was confirmed by comparison to the structure of **168** reported by Husson (Scheme 28). In the case of the 2,6-*cis* cycloadduct (**166a**) it was difficult to assign J-couplings since there was significant overlap with the resonances of the 2,6-*trans* cycloadduct (**166b**). Note that although commercially available diene **161** is contaminated with ca. 30% of 4-methylpentadiene, we only observe a reaction of **161** as the Z-diene isomer does not undergo a Diels-Alder reaction.

Scheme 28



The final entry in Table 1 shows the cycloaddition of *N*-benzyliminoacetonitrile with cyclohexadiene. We observed only a fair yield of the desired cycloadduct **167** using either method A or B. We also attempted the cycloaddition with cycloheptadiene and observed no cycloadduct. We attribute the low yield with cyclohexadiene (and no reaction with cycloheptadiene) to steric effects. The iminoacetonitrile has to overcome the steric repulsion of the methylenes on each diene to achieve proper overlap of orbitals.

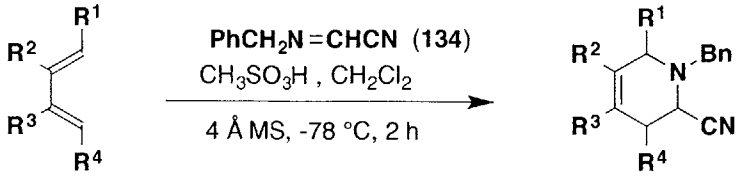
Another common unactivated diene used in Diels-Alder reactions is 1,2-dimethyl-butadiene. Unfortunately, under the optimized conditions developed in the previous cycloadditions we observed a mixture of products. Two regioisomeric cycloadducts were observed, both as a mixture of cyano epimers. Another byproduct of this reaction was the "ene-type" product **174** (eq 34). Bailey and coworkers reported a similar byproduct in their 2002 paper on intermolecular cycloadditions with benzhydryl imines.[16]

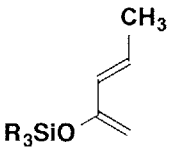
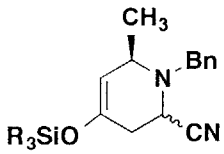
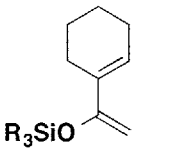
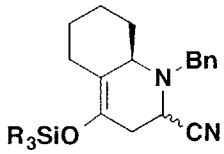
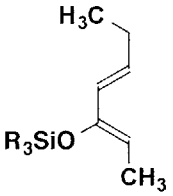
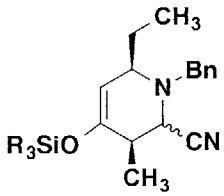
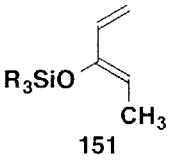
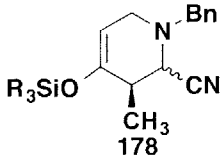


Silyloxy Dienes

Following the success of our study of aza Diels-Alder reactions of **134** with simple unactivated dienes, we next turned our attention to silyloxy-substituted dienes. An important goal here was to demonstrate the use of *tert*-butyldimethylsilyloxy groups to direct the regioselectivity of the reaction so as to selectively install groups around the piperidine ring. Table 2 shows several silyloxy dienes that participate in the aza Diels-Alder reaction with *N*-benzyliminoacetonitrile **134**. Silyl enol ethers are more activated 4π partners than the previously described dienes, and the competitive polymerization of the dienes was not found to be a significant problem during these cycloadditions. Consequently, similar yields were observed using either method A or B for the Diels-Alder reactions of these activated dienes. We were pleased to observe that at the low reaction temperature (-78 °C) there was reaction of the acid with the silyl enol ether cycloadducts or diene. Using excess MsOH (method B) did not reduce the yield of the silyl enol ether cycloadducts. Entries 3 and 4 in Table 2 show yields comparable to that of the cycloadditions with unactivated dienes.

Table 2. Intermolecular [4 + 2] Cycloadditions of *N*-Benzyliminoacetonitrile with Silyl Enol Ethers



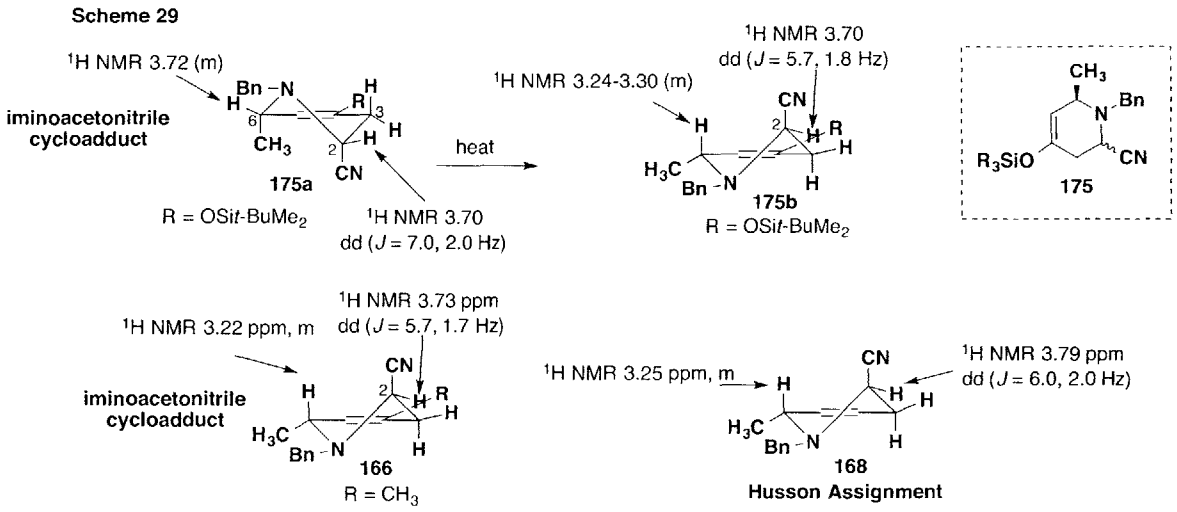
entry	diene	cycloadduct	yield (%)[a] method A	yield (%)[a] method B
1	 **141**	 **175**	51-53	50
2	 **144**	 **176**	57	46
3	 **148**	 **177**	75-82	-
4	 **151**	 **178**	70-74	-

R_3Si = *t*-$BuMe_2Si$

[a] Isolated yield of products purified by chromatography. Method A: 1.0 equiv MsOH, 1.5 equiv diene. Method B: 1.5 equiv MsOH, 4.0 equiv diene.

The aza Diels-Alder reaction of **134** with diene **141** installs a methyl group at C6 of the cycloadduct (**175**). This cycloaddition yields a mixture of cyano epimers in moderate yield as a

59:41 mixture of cyano epimers. Unlike the cases shown in Table 1, using additional diene does not improve the yield of this reaction. By equilibrating the epimers to the more stable product, we were able to use ^{1}H NMR analysis to determine the relative stereochemistry of the substituents. Scheme 29 compares our cycloadduct **175** to a previously assigned cycloadduct **166** and one of the tetrahydropyridines (**168**) assigned by Husson. In **175a**, H2 has 7.0 and 2.0 Hz coupling constants, supporting its position in the equatorial orientation and coupling to both equatorial and axial protons. There is excellent agreement between the ^{1}H NMR data between tetrahydropyridines **175b**, **166**, and **168** with regard to the data for the protons at C2 and C6.

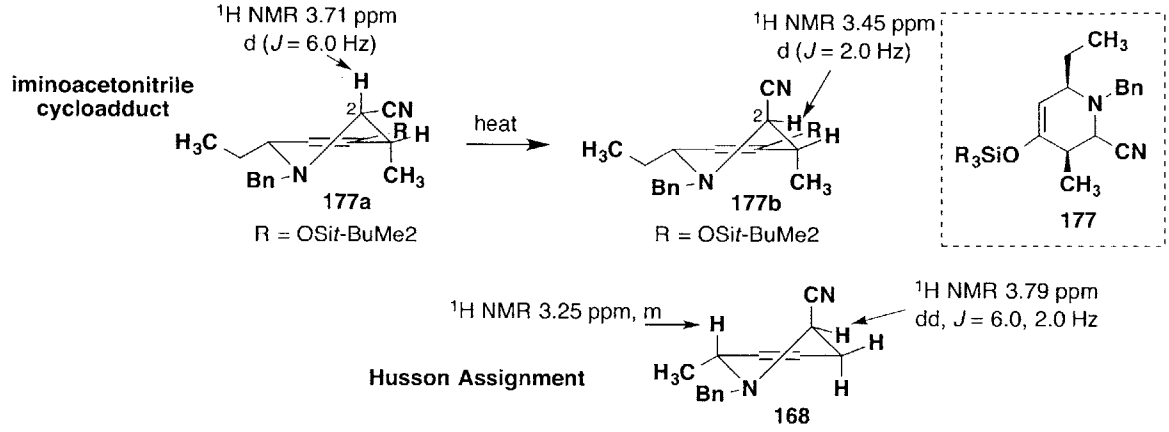


To synthesize a bicyclic structure using the intermolecular aza Diels-Alder reaction, we reacted diene **144** with *N*-benzyliminoacetonitrile to afford cycloadduct **176** in moderate yield as the usual mixture of inconsequential cyano epimers (61:39). Again, the optimized conditions for this cycloaddition involve only 1 equiv of MsOH and 1.5 equiv diene at -78 °C.

If two different substituents at C3 and C6 are required in a target molecule then a silyloxy group can be employed to direct the regiochemical course of cycloaddition as illustrated in entry 3 in Table 2. In this case, we were able to install an ethyl group at C6 and a methyl substituent at C3 with excellent regioselectivity. The initially formed two cyano epimers were equilibrated to

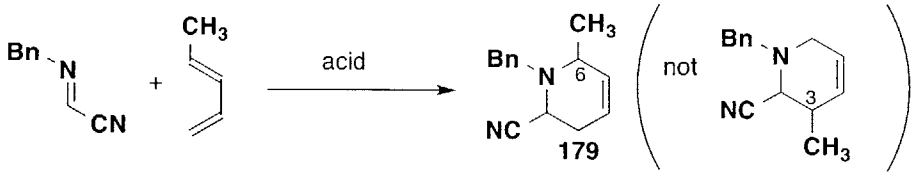
confirm the stereochemical assignments shown in Scheme 30. The J-value (6.0 Hz) represents the axial-equatorial coupling between protons in **177a**. Upon epimerization of the cyano group to the axial orientation, a small J-value is observed (2.0 Hz) for the equatorial-equatorial coupling.

Scheme 30



As illustrated with the reaction shown in eq 34 on page 67, the cycloaddition of iminoacetonitriles with 3-methyl-1,3-pentadiene afford a mixture of regioisomers. Formation of a cycloadduct with a substituent at C3 in high regioselectivity is not trivial using the Diels-Alder reaction since the predicted regioisomer puts a substituent at C6 (Scheme 31).

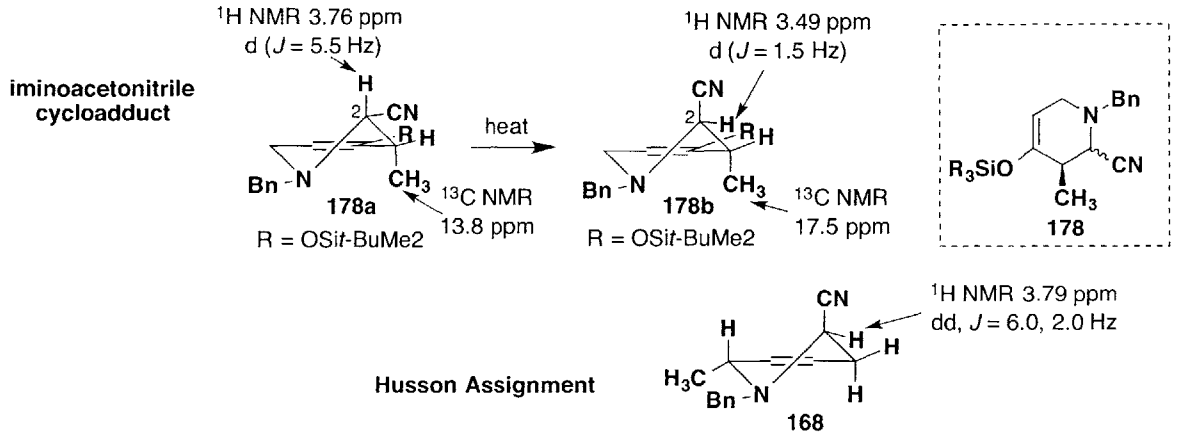
Scheme 31



Using silyloxy dienes such as **151** we can overcome this challenge and install a group at C3 in the absence of a substituent at C6 using the silyloxy group to direct the regiochemistry. Cycloadduct **178** is formed in 70-74% yield as a mixture of cyano epimers. Scheme 31 shows the ^{1}H NMR data for the C2 hydrogen. The major cycloadduct **178a** is the endo product with

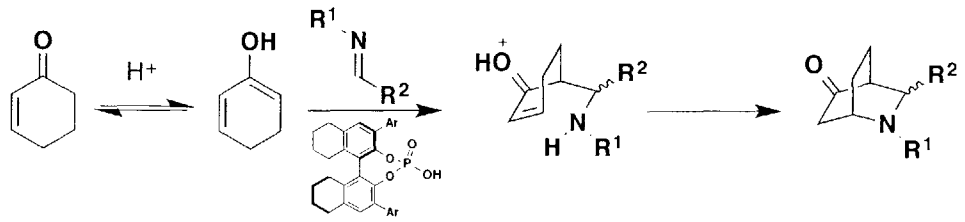
respect to the cyano group. Upon equilibration, additional **178b** is formed with the cyano group axial and a 1.5 Hz coupling constant is observed suggesting an equatorial-equatorial relationship between the protons at C2 and C3.

Scheme 32



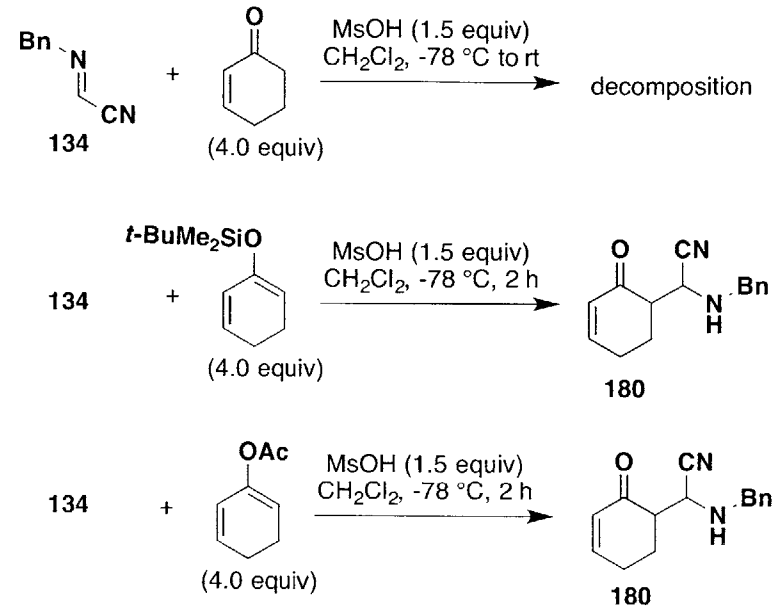
Other oxygen-substituted dienes were screened in this cycloaddition. Gong and coworkers showed that cyclohexenone can be a viable 4π component in aza Diels Alder reactions.[45c] The enol tautomer of this enone is generated in situ in the presence of a Brønsted acid and then participates in a stepwise [4 + 2] cycloaddition (Scheme 33).

Scheme 33



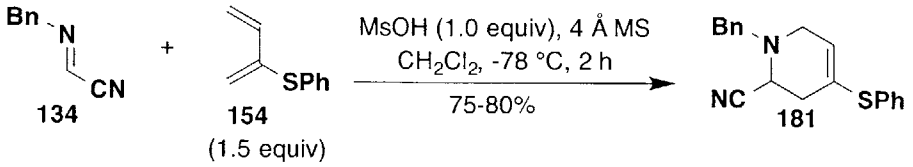
We explored the reactivity of cyclohexenone in an aza Diels-Alder reaction with *N*-benzyliminoacetonitrile but observed complete decomposition of the iminoacetonitrile and no cycloadduct. Pre-forming an enol ether derivative also did not favor the cycloaddition and instead we observed the 1,2-addition product **180** (Scheme 34).

Scheme 34



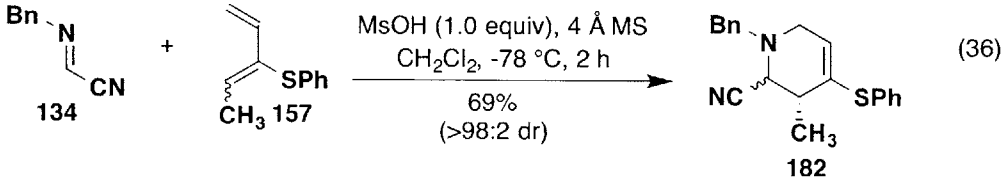
Phenylthio-Substituted Dienes

As mentioned earlier, sulfur-substituted dienes were of interest in our study because of the possibility of cleaving them at a later stage in a synthesis to produce piperidines that would not be available by direct cycloadditions. The aza Diels-Alder reaction between diene **154** and iminoacetonitrile **134** furnishes α-amino nitrile **181** in good yield. Only 1.5 equiv of diene is required to obtain a reproducible yield for the cycloaddition shown in eq 35. The following chapter will describe a method for the cleavage of vinyl sulfides of this type using Raney nickel to afford piperidines with only C2 alkyl substitution.



(35)

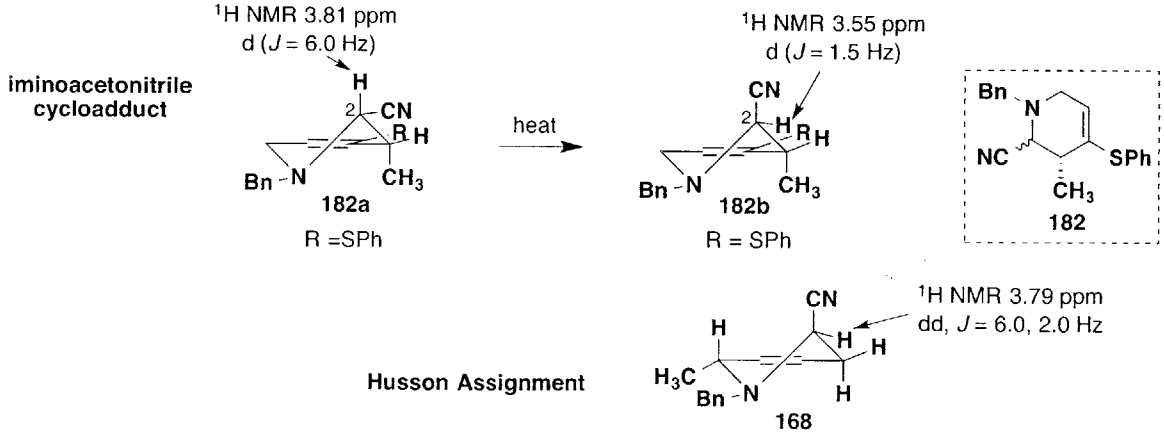
The final diene used to explore the scope of the intermolecular [4 + 2] cycloaddition of *N*-benzyliminoacetonitrile was 3-phenylthio-1,3-pentadiene (**157**). The cycloaddition of imine **134** with 1.5 equiv of diene **157** proceeded in good yield after the addition of 1.0 equiv of MsOH at low temperature (eq 36). As observed in many of the other cycloadditions, the product was isolated as a mixture of cyano epimers that equilibrate to the thermodynamic product with the nitrile in the axial position.



(36)

Scheme 34 shows the ^{1}H NMR data for the proton at C2. The kinetic product **182a** has a coupling constant of 6.0 Hz between the protons at C2 and C3. After equilibration, the J-value is 1.5 Hz, suggesting an equatorial-equatorial relationship in **182a** between H2 and H3.

Scheme 35



Stereochemical Assignment of Cycloadducts.

Throughout this chapter the stereochemistry of the cycloadducts was assigned by comparison to known compounds found in the literature. These comparisons are a good

indication of the stereochemical relationship between the substituents on the tetrahydropyridine rings. Many of the cycloadducts can also be compared to each other in order to predict and confirm stereochemical assignments. In addition to comparing substrates, there is another method for the determination of relative stereochemistry on the piperidine ring system using the benzyl methylene protons as an indicator of the symmetry of the molecule. This method was first reported by Hill and Chan in 1965.[81] Diastereotopic protons are not chemically equivalent and couple to each other. For example, Hill and Chan report the ^{1}H NMR spectra for 2,6-*cis* and 2,6-*trans* *N*-benzyldimethyl piperidine. The benzylic methylene protons appear as an AB quartet for the 2,6-*trans* piperidine and a singlet for the 2,6-*cis* piperidine (Figure 8). The ^{1}H NMR spectrum conveys the difference in the environment for each benzylic proton.

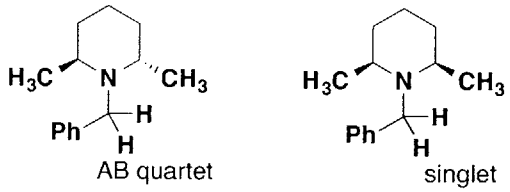


Figure 8

Husson and coworkers used this approach to determine the relationship of substituents on a tetrahydropyridine ring system. In compounds **183** and **184**, the benzylic protons appear as well separated AB quartets where $\Delta\delta_{AB}$ = 0.24 ppm. When the tetrahydropyridines are more symmetrical, the AB quartets begin to appear more like singlet resonances such as in the ^{1}H NMR spectra of **185** and **186.**

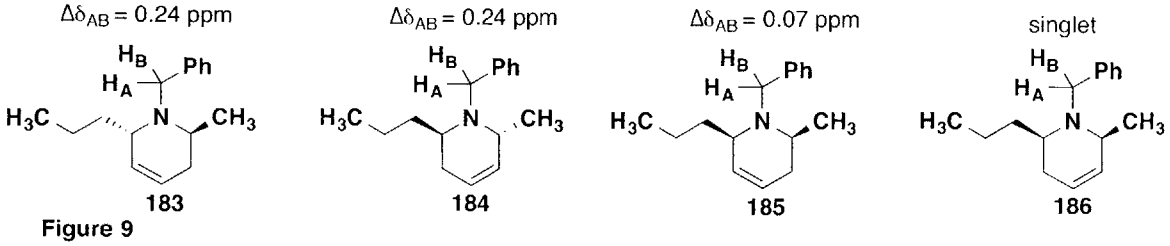


Figure 9

[81] Hill, R. K.; Chan, T. *Tetrahedron* **1965**, *21*, 2015-2019

To better understand the topicity of the benzyl protons Husson showed possible Newman projections of our 6-alkyl-α-amino nitrile cycloadducts where the cyano group is axial in all cases (Figure 10).[78] When R^1 is an equatorial alkyl group (2,6-trans piperidine), the lowest energy conformation is **187b**, where the phenyl ring is far from the R1 group. This conformation places H_A and H_B in very different chemical environments, resulting in an AB quartet with a large $\Delta\delta_{AB}$. When the alkyl group is R^2 (2,6-cis piperidine), conformation **187a** and **187b** are both possibilities since there is not a significant energy difference between either conformation based on the two possible environments for H_B and H_A. The similar environments for the benzylic protons between **187a** and **187b** results in the benzyl protons becoming either a singlet in the ^{1}H NMR or an AB quartet with a small $\Delta\delta_{AB}$.

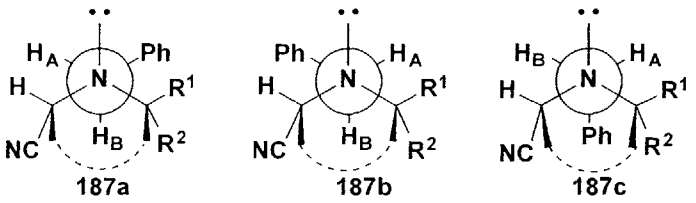


Figure 10

Husson also noticed a trend in the ^{13}C NMR spectrum for similar compounds. Compounds with the 2,6-*trans* relationship shifted the benzyl carbon upfield due to the γ-effect of having a substituent axial on the ring, shielding the benzyl carbon. The difference between the benzyl carbon resonance of the *cis* and *trans* piperidines is ca. 5-6 ppm.

Using symmetry and nuclear magnetic resonance spectroscopy to further support our structure assignments have been a great tools not only in determining the structures of our cycloadducts, but also determining the structures of the piperidine ring systems formed in the next section.

Summary

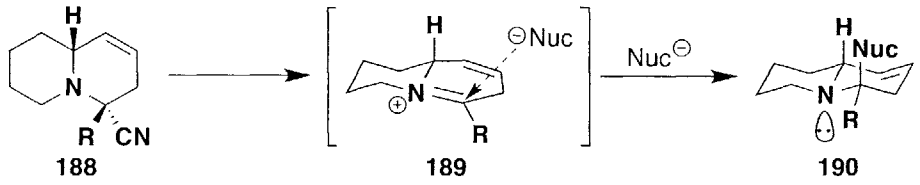
In summary, iminoacetonitriles are excellent dienophiles in both *intra*molecular and *inter*molecular [4 + 2] cycloadditions. We have developed a reliable and efficient method for the synthesis of *N*-benzyliminoacetonitrile and showcased its reactivity in cycloaddition reactions with a variety of dienes. In the next chapter we explore the synthetic utility of the α-amino nitrile cycloadducts to access a wide variety of substituted tetrahydropyridines.

Chapter 2

Transformations of α-Amino Nitrile Cycloadducts

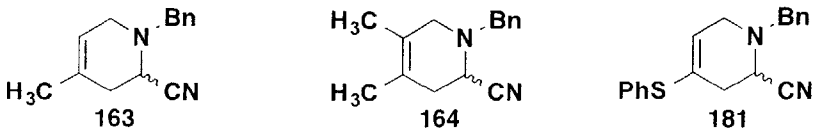
After determining the scope of the intermolecular [4 + 2] cycloaddition of *N*-benzyliminoacetonitrile, it was important to show the synthetic utility of the resulting cycloadducts. We investigated the synthetic elaboration of these α-amino nitriles using both the Bruylants reaction and an alkylation/reductive decyanation strategy. Our group has previously developed analogous transformations of quinolizidine cycloadducts with great success. Stereoelectronic control governs the stereochemical outcome of these reactions, with the nucleophile approaching the iminium ion antiperiplanar to the developing lone pair on the nitrogen (Scheme 36).[47] In the case of quinolizidines, this results in the formation of products in which the new substituent has an axial, exo orientation on the bicyclic ring.

Scheme 36



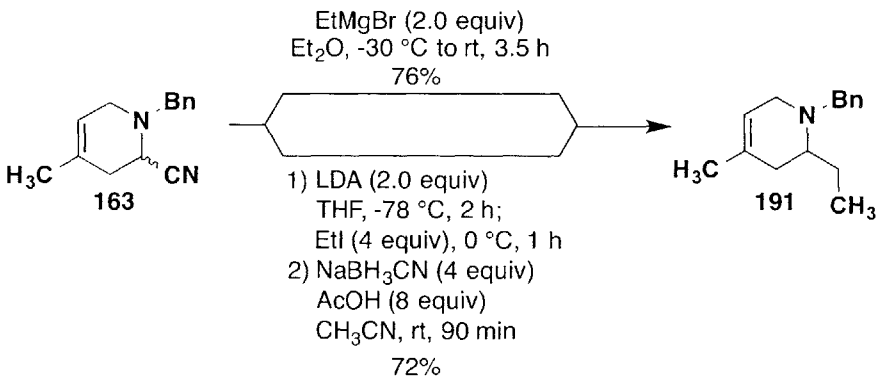
Transformations of 4-Substituted and 4,5-Disubstituted Cycloadducts

Piperidines **163**, **164**, and **181** were among the cycloadducts whose transformations we studied. In these cases there is no stereochemical ambiguity with regard to the structures of the products of Bruylants reactions and alkylation/reductive decyanation.



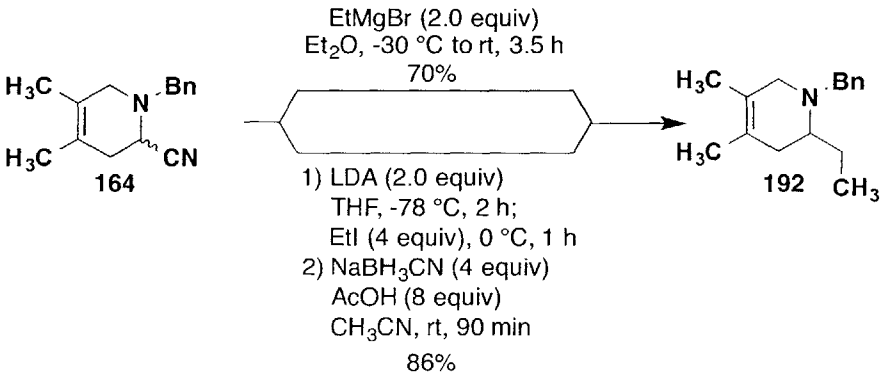
The Bruylants reaction of **163** with ethylmagnesium bromide affords **191** in 76% yield (Scheme 37). As usual, due to the Lewis acidic Mg^{2+} species present in ethylmagnesium bromide solution, an iminium ion is generated under the reaction conditions from the α-amino nitrile. Attack on the iminium ion by the carbon nucleophile results in an overall substitution product in good yield. Excess Grignard reagent is required or a significant decrease in yield is observed. Scheme 37 also illustrates another method we have used to elaborate our α-amino nitrile cycloadducts. Metalation of **163** with lithium diisopropylamide followed by the addition of ethyl iodide results in a tertiary amino nitrile. In most cases employing less than 2 equiv of LDA results in unreacted α-amino nitrile. Following workup of the alkylation reaction, the crude product is added to a mixture of sodium cyanoborohydride and AcOH to afford **191** in 72% yield. The reductive decyanation conditions used here were previously developed for the quinolizidine cycloadduct substrates. All yields reported for the alkylation/reductive decyanation are reported over two steps, because the tertiary amino nitrile is not purified before reductive decyanation due to its instability to silica gel.

Scheme 37



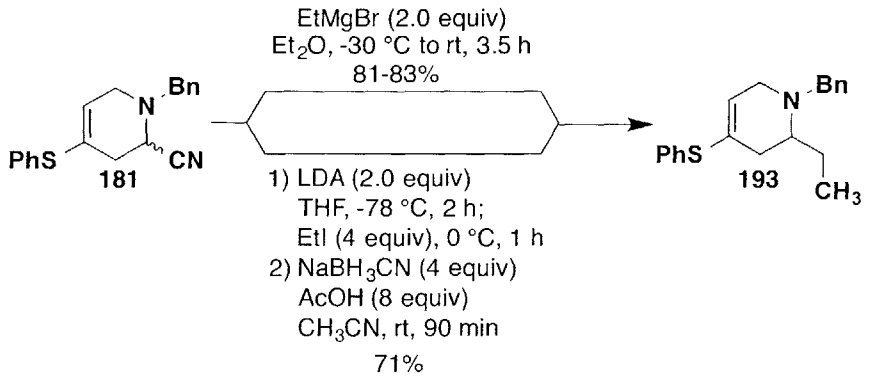
Cycloadduct **164** participates in the same transformations as shown in Scheme 38. Both the Bruylants reaction and alkylation followed by reductive decyanation afford **192** in good to excellent yield.

Scheme 38



The vinyl sulfide cycloadduct (**181**) also participates in both transformations to afford **193** in good yield as shown in Scheme 39. The reduction of the vinyl sulfide using Raney nickel is discussed later in this chapter.

Scheme 39

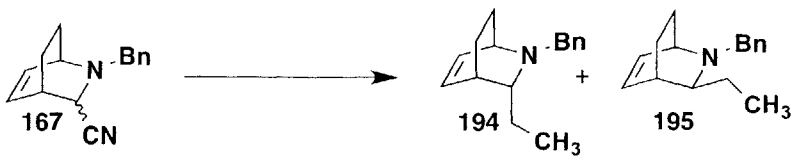


Transformations of the [2.2.2] Bicyclic Cycloadduct

Cycloadducts with stereocenters are more interesting substrates for the demonstration of the reactivity of α-amino nitriles. The relative stereochemistry of the substituents on the ring play a significant role in determining the lowest energy conformation of the tetrahydropyridine ring, as well as influencing the lowest energy transition state for nucleophilic attack on the iminium ion. The 2-aza-bicyclo[2.2.2]octane cycloadduct (**167**) was an excellent substrate to investigate diastereoselectivity of both the Bruylants reaction and the alkylation/reductive decyanation reactions.

The Bruylants reaction of cycloadduct **167** with ethylmagnesium bromide results in one diastereomer **194** in moderate yield. Entry 2 in Table 3 shows the result of employing the alkylation/reductive decyanation method. After initial alkylation of cycloadduct **167,** we isolated the tertiary amino nitrile following work up and immediately subjected it to the reductive decyanation conditions to afford a 75:25 mixture of **195** and **194** in good yield. This method favors diastereomer **195** with stereochemistry opposite to that of the Bruylants product.

Table 3. Transformations of 2-Aza-bicyclo[2.2.2]octane Cycloadduct



entry	conditions	**194**:**195** ratio	yield[a]
1	EtMgBr (2.0 equiv) Et_2O, -30 °C to rt, 3.5 h	>99:1	66-67%
2	1) LDA (2.0 equiv), THF 2 h, -78 °C; EtI (4 equiv), 0 °C, 1 h 2) $NaBH_3CN$ (4 equiv), AcOH (8 equiv) THF, rt, 1.5 h	25:75	71-74%

[a] Isolated yield of products purified by column chromatography.

Nucleophilic attack of the iminium ion is favored to occur from the alkene side of the iminium ion, which is less sterically hindered (Figure 11). The small hydride nucleophile is less selective for the reactive face of the iminium ion as one would expect, eroding the dr of the products as reported entry 2. In a monocyclic substrate ethylmagnesium bromide showed higher stereoselectivity than methylmagnesium bromide, showing that the size of the nucleophile does play a role in the degree of diastereoselectivity.

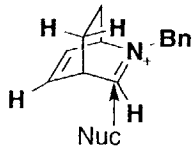
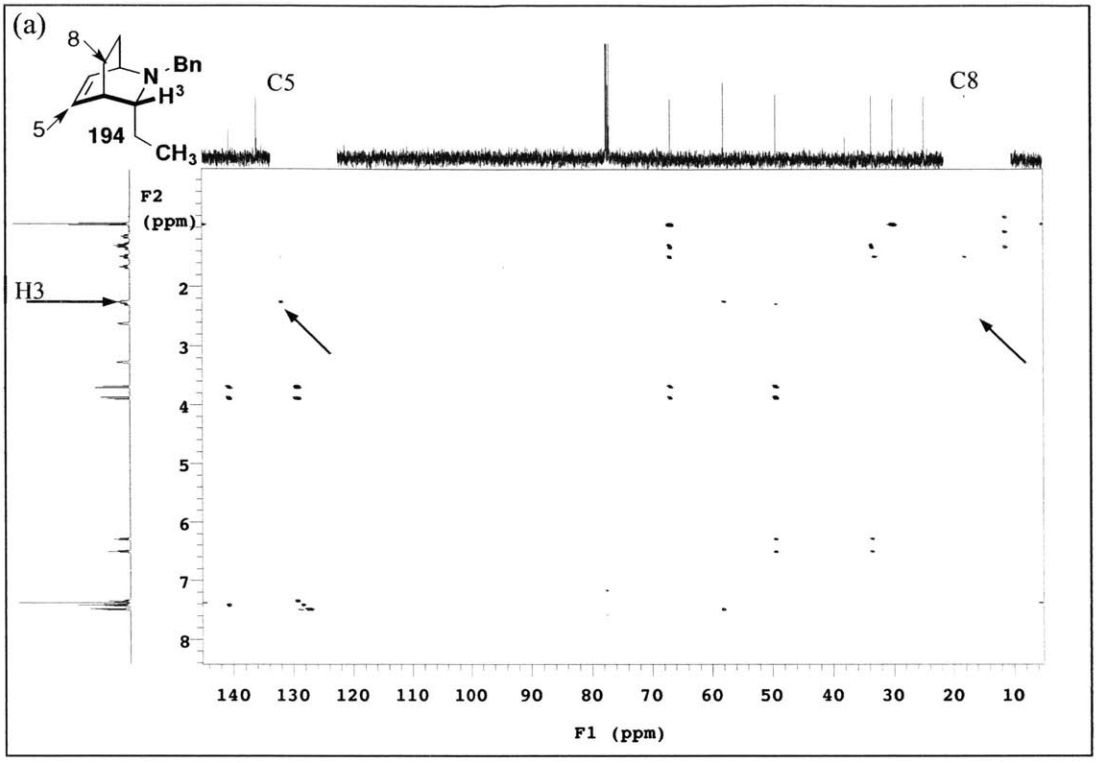


Figure 11

NMR analysis of **194** and **195** was used to assign the relative stereochemistry of the ethyl substituent. After assignment of all carbon and proton resonances from the proton, carbon, gCOSY, HSQC, and HMBC spectra for **194**, we looked for a key cross peak in the HMBC spectrum. A strong *trans* ^{3}J-coupling in the HMBC spectrum between H3 and C5 supports the assignment of **194** as being the major product from the Bruylants reaction. For *trans* (180°) couplings, the ^{3}J has a large value (8-10 Hz) so we are able to see a strong cross peak in the

HMBC.[82] A cross peak between H3 and C8 of **194** is not observed in the HMBC (Figure 12a). We also assigned proton and carbon resonances for the other isomer **195**. Likewise, a strong *trans* ^{3}J-coupling in the HMBC spectrum between H3 and C8 supports the assignment of **195** as the major product from the alkylation reductive decyanation reaction (Figure 12b). In the case of **195** there is no cross peak between H3 and C5 in the HMBC.

[82] For discussion of 2D NMR, see; Simpson, J. H. *Organic Structure Determination Using 2-D NMR Spectroscopy*, Elsevier Inc: Oxford, UK, 2008, pp 178-181.



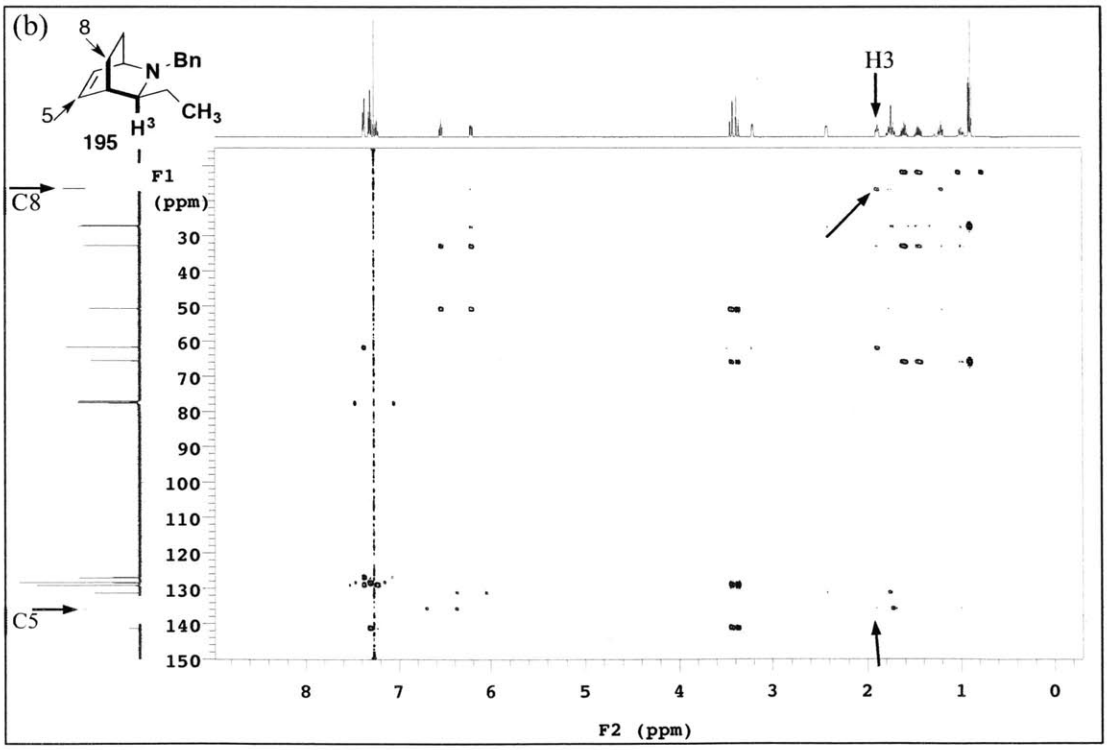
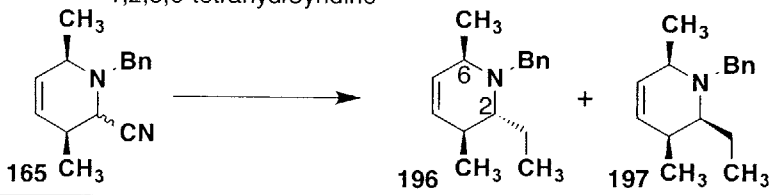


Figure 12. HMBC of **194** and **195**

Diastereoselective Transformations of Monocyclic Cycloadducts

We also observed high diastereoselectivity in the transformations of cycloadduct **165** (Table 4). The Bruylants reaction of **165** with ethylmagnesium bromide resulted in one diastereomer (**196**) in 84% yield. Alkylation of **165** by metalation with LDA followed by the addition of ethyl iodide proceeded smoothly. Isolation of the crude tertiary amino nitrile followed by reductive decyanation afforded an 80:20 mixture of 2,6-*cis* (**197**) and 2,6-*trans* tetrahydropyridines (**196**). Reductive decyanation with $NaBH_3CN$/AcOH or Na/NH_3 resulted in similar ratios of products as shown in Table 4. Reductive decyanation using $NaBH_3CN$ generally represents the optimal procedure for our cycloadducts, but note that dissolving metal conditions can be a useful option for reductive decyanation when the substrates are acid sensitive.

Table 4. Transformations of *N*-Benzyl-2-cyano-3,6-dimethyl-1,2,3,6-tetrahydroyridine



entry	conditions	**196:197** ratio	yield (%)[a]
1	EtMgBr (2.0 equiv) Et_2O, -30 °C to rt, 3.5 h	>99:1	84
2	1) LDA (2.0 equiv), THF 2 h, -78 °C; EtI (4 equiv), 0 °C, 1 h 2) $NaBH_3CN$ (4 equiv), AcOH (8 equiv) THF, rt, 1.5 h	20:80	73
3	1) LDA (2.0 equiv), THF 2 h, -78 °C; EtI (4 equiv), 0 °C, 1 h 2) Na (10 equiv), NH_3 (l) -78 °C, 5 min	25:75	58

[a] Isolated yield of products purified by column chromatography.

It was very important to assign the correct relative stereochemistry for the two diastereomers. The signals for the benzylic carbons in tetrahydropyridines **196** and **197** are ca. 4.3 ppm apart. The benzylic carbon of the 2,6-*trans* product **196** (51.6 ppm)[83] appears upfield from the 2,6-*cis* isomer (55.9 ppm) as expected due to the γ-effect[84] where a substituent is forced into the axial position shielding the benzylic carbon.

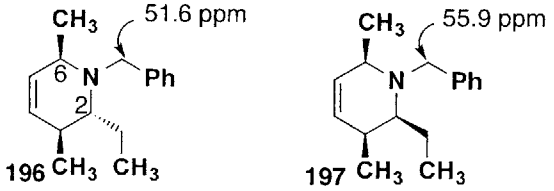


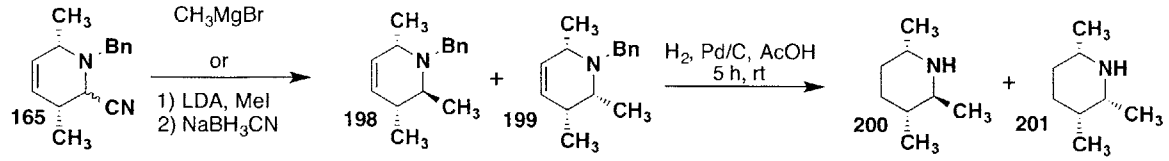
Figure 13

Besides interpreting coupling constants and ^{13}C NMR shifts for the tetrahydropyridines, we attempted to synthesize a known piperidine using our method. Further confirmation of the assignments of **196** and **197** came from our preparation of the analogous methyl-substituted piperidines **198** and **199**. Hydrogenation of the olefin and hydrogenolysis of the *N*-benzyl protecting group in a single step afforded the desired two piperidines **200** and **201** (Scheme 40). Trimethylpiperidine **201** was previously synthesized by both LeBel[85] and Liebeskind[86] using two different methods. As discussed below, comparison of the NMR data for our synthetic compounds with that reported by LeBel and by Liebeskind suggested that the Bruylants reaction had led to predominately **200**, while the alkylation/reductive decyanation produced **201** as the major product.

---

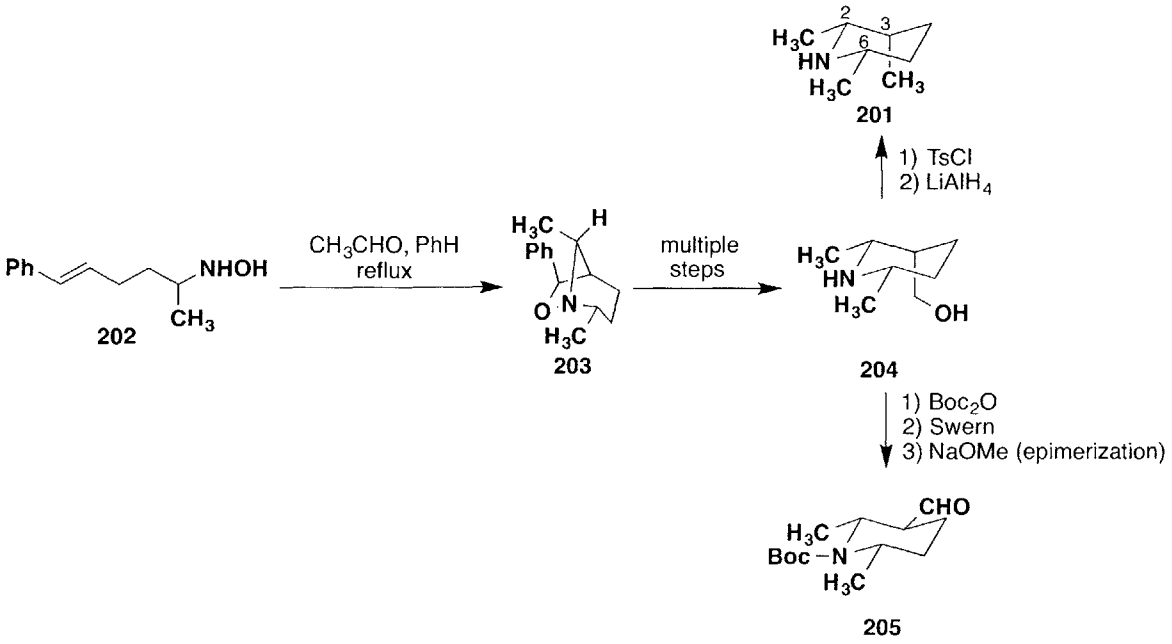
[83] Carbon resonance assigned by HSQC.
[84] For discussion of the γ-effect, see: Pihlaja, K.; Kleinpeter, E. *Carbon-13- NMR Chemical Shifts in Structural and Stereochemical Analysis, Marchand, A. P. Ed.;* VCH Publishers, INC.: New York, NY, 1994; pp 58-71.
[85] LeBel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363-3368.
[86] Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477-12487.

Scheme 40



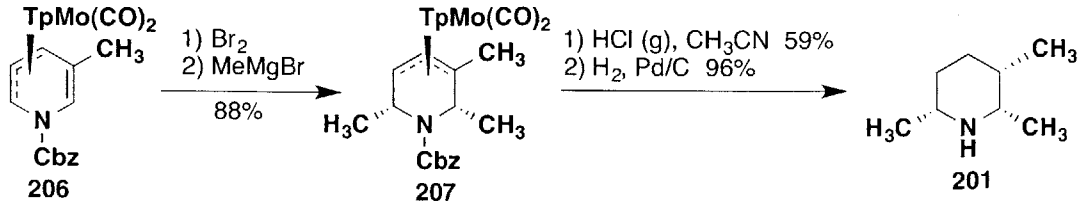
In 1989 LeBel synthesized **201** via a bicyclic isoxazolidine (Scheme 41). The structure of **203** was proven by J-values in the ^{1}H NMR spectrum and the chemical shifts of the methyl group at the bridgehead that is shielded by the aromatic ring. Reduction of the isoxazolidine in several steps afforded all-cis piperidine **204**. Coupling constants in the ^{1}H NMR spectrum also suggest the equatorial orientation for the substitutes at C2 and C6, and an axial orientation for the substituent at C3. To assign the relative stereochemistry, LeBel formed the aldehyde and epimerized the center to the thermodynamically more favorable isomer **205** with all equatorial substituents. LeBel also synthesized 2,3,6-trimethylpiperidine **201** and used ^{13}C NMR spectroscopy to assign the structure. Carbon resonances at C2 and C6 suggest equatorial substituents and the carbon at C3 suggests it adopts the axial orientation.

Scheme 41



Liebeskind synthesized **201** via a different method. He unambiguously assigned the stereochemistry of **201** and then used it to make relative stereochemical assignments for other products produced by his method. Enantiopure $TpMo(CO)_2$(pyridinyl) complexes were used to prepare trisubstituted piperidines. The reaction conditions for the demetalation dictate whether a 2,3,6-*cis* or 2,6-*cis*-3-*trans*-trisubstituted piperidine results. Protodemetalation provided the all-*cis*-piperidine as shown in Scheme 42. Liebeskind proposed that protodemetalation proceeds by protonation of the metal center with HCl. Reductive elimination of the cationic molybdenum complex yields the 2,3,6-*cis*-trimethyl-4-5-didehydropiperidine. Reductive demetalation using $NOPF_6$ and $NaCNBH_3$ affords the 2,6-*cis*-3-*trans* piperidine via hydride addition from the opposite face of the ring. The reductive demetalation strategy was used for synthesis of known indolizidine 209B, which has the 2,6-*cis*-3-*trans* stereochemical relationship.

Scheme 42



The spectral data for our synthetic piperidines and the data reported by LeBel and Liebeskind are shown in Table 5. The ^{1}H NMR data was not satisfactory for assignment of the structures. The proton resonances of our compounds did not correspond closely with values reported by LeBel and by Liebeskind, presumably due to variations in chloroform acidity and small impurities in the samples. On the other hand, the ^{13}C NMR spectra showed good agreement with the literature values as summarized in Table 5.

Table 5. ^{13}C NMR comparison for 2,3,6-trimethylpiperidine

Carbon	**201** Proposed 2,6-cis isomer[87]	**200** Proposed 2,6-trans isomer[87]	**201** LeBel[85,88]	**201** Liebeskind[86,89]
1	54.8	51.3	54.3	54.7
2	53.2	47.2	52.8	53.1
3	32.5	38.2	34.6	31.2
4	32.0	31.2	33.6	31.0
5	28.9	28.1	31.2	26.9
6	23.2	21.1	22.4	20.9
7	20.5	19.3	22.1	18.4
8	11.3	19.2	12.2	11.2

Although the carbon data does suggest that the major product of the alkylation/reductive decyanation reaction is **201**, more evidence was desired in order to be satisfied with the assignments. Note that **201** would result from hydride attack on the iminium ion from the side

[87] NMR recorded in $CDCl_3$ referenced to 77.23 ppm.
[88] NMR recorded in $CDCl_3$.
[89] NMR recorded in $CDCl_3$ refererenced to 77.30 ppm.

opposite the methyl substituents. The stereochemical outcome of Bruylants reactions with C3 alkyl-substituted tetrahydropyridines is further confirmed by a NOE difference experiment, which will be discussed on page 100 with regard to another case that we studied.

As mentioned above, bicyclic cycloadduct **167** and α-amino nitrile **165** show excellent diastereoselectivity in the Bruylants reaction and alkylation/reductive decyanation. However, we observed very different results when an alkyl substituent is not present at C3 as in the case of cycloadduct **166** (Table 6). 2,6-*cis* Tetrahydropyridine **210** is the major product using either the Bruylants reaction or alkylation/reductive decyanation methods. A relatively low yield was obtained for the alkylation/reductive decyanation sequence shown in entry 2. In this case we observed the formation of several byproducts, including the 1,2,5,6-tetrahydropyridine resulting from migration of the olefin in the six-membered ring to form **208**. Performing the reductive decyanation under dissolving metal conditions avoids the formation of this isomerization product and provides the desired products in improved yield.

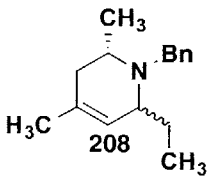
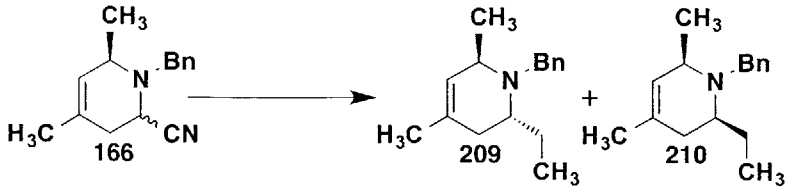


Figure 14

Table 6. Transformations of *N*-Benzyl-2-cyano-4,6-dimethyl-1,2,3,6-tetrahydroyridine



entry	conditions	**209:210** ratio	yield (%)[a]
1	EtMgBr (2.0 equiv) Et_2O, -30 °C to rt, 3.5 h	40:60	80
2	1) LDA (2.0 equiv), THF 2 h, -78 °C; EtI (4 equiv), 0 °C, 1 h 2) $NaBH_3CN$ (4 equiv), AcOH (8 equiv) THF, rt, 1.5 h	40:60	48
3	1) LDA (2.0 equiv), THF 2 h, -78 °C; EtI (4 equiv), 0 °C, 1 h 2) Na (10 equiv), NH_3 (l) -78 °C, 5 min	35:65	66

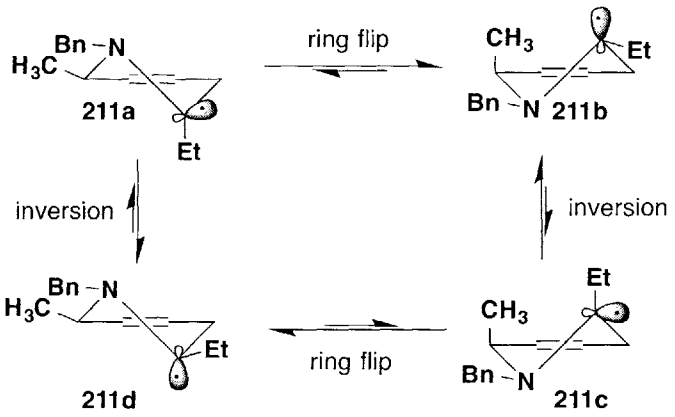
[a] Isolated yield.

For entries 1 and 2 in Table 6, the reaction proceeds through an iminium ion. With few bulky groups on the ring, we speculate there is not a strong bias for the nucleophilic attack from one face over the other, since the substituent at C6 is far from the reacting center of the iminium ion.

Reductive decyanation under dissolving metal conditions follows an alternate mechanism that was described in Part I in Scheme 20. It is believed that the mechanism proceeds through a carbon centered radical as shown in Scheme 43. The stereochemistry of the products is determined by which radical is reduced to an anion that is then rapidly protonated. The two most stable radical conformations are **211b** and **211d** where the unpaired electron is axial and oriented

for stabilization by delocalization involving the nitrogen lone pair. The low dr under these conditions may be due to there being a the small difference in energy between **211b** and **211d**, as well as the expectation that these radicals are rapidly interconverting by inversion and "ring flipping" of half-chair conformers.[90]

Scheme 43



We were surprised by the low diastereoselectivity observed in some of our cases. As discussed below, there have been a number of reports of related reactions of cyclic α-amino nitriles that proceed with high diastereoselectivity.[91]

In 1999, Schneider and coworkers investigated the reactions of several α-amino nitriles with carbon nucleophiles (Scheme 44).[92] The only difference between α-amino nitriles **212** and **215** is the stereochemistry of the methyl group at C5. This small difference in substituent orientation leads to a difference in diastereoselectivity from 1:1 to 10:1.

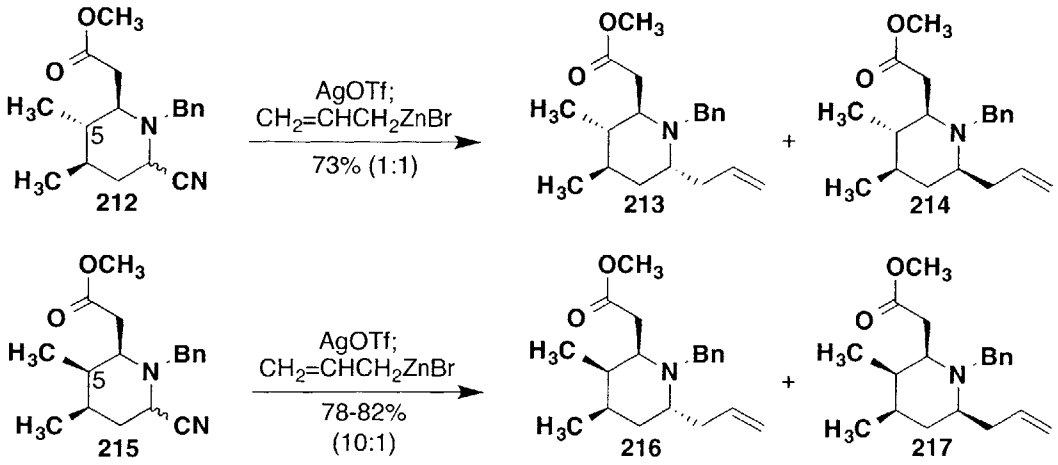
---

[90] Cyclohexyl radical has a conformational-inversion barrier of ca. 5.5 kcal/mol. Radical inversion between two axial oriented radicals has a estimated barrier of ≤0.5 kcal/mol. (a) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386-9390. (b) Griller, D.; Ingold, K. U.; Krusic, P. J.; Fischer, H. *J. Am. Chem. Soc.* **1978**, *100*, 6750-6752. (c) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2025-2029.

[91] For selected examples of stereocontrolled addition to iminium ions, see: (a) Reference 49. (b) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198-8207. (c) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064-4067. (d) Duttwyler, S.; Chen, S.; Takase, M. K.; Wilberg, K. B.; Bergman, R. G.; Ellman, J. A. *Science* **2012**, *339*, 678-682. (e) Ischay, M. A.; Takase, M. K.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 2478-2381.

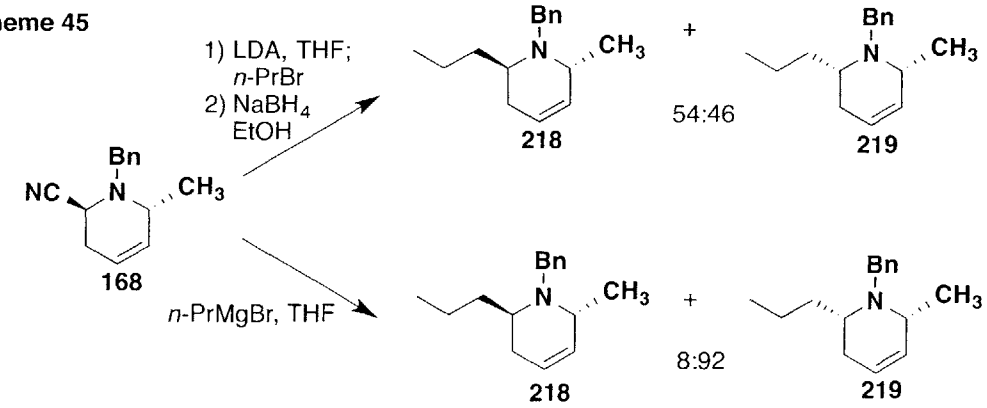
[92] Schneider, C.; Börner, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1999**, 3353-3362.

Scheme 44



In 1984, Husson and coworkers described the transformations of **168** shown in Scheme 45 involving alkylation/reductive decyanation and Bruylants reaction.[78] Alkylation/reductive decyanation resulted in a 54:46 ratio of tetrahydropyridines **218** and **219**. However, using a carbon nucleophile resulted in an 8:92 mixture of the same products. In this case, the carbon nucleophile afforded high diastereoselectivity in the transformation, but the authors were not able to rationalize the large difference in selectivity between the two reactions.

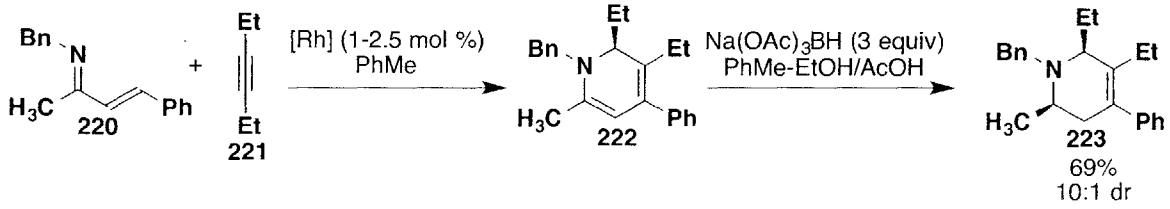
Scheme 45



Another report in the literature where poor diastereoselectivity (65:35) was observed for reductive decyanation with sodium borohydride was in a synthesis of solenopsin A.[93] The results of these transformations seem to be dependent on the substituents on the ring, including the nitrogen substituent. Clearly another factor affecting selectivity is whether or not a double bond is present in the piperidine ring. Our systems are tetrahydropyridines, which we expect to adopt a different conformation compared to saturated piperidines.

In 2012 and 2013, Ellman and workers[91b,c,d] reported an efficient synthesis of highly substituted tetrahydropyridines via a rhodium-catalyzed synthesis of dihydropyridines followed by nucleophilic trapping of iminium ions derived from these compounds. The ring systems they report all have a higher degree of substitution than our substrates, and the iminium ion was generated in situ via isomerization of the dihydropyridine. Ellman reports the use of $NaBH(OAc)_3$ as the reducing agent of choice to obtain optimal diastereoselectivity (Scheme 46).

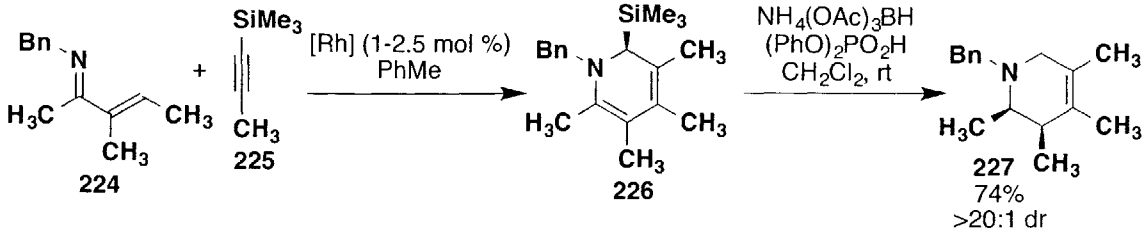
Scheme 46



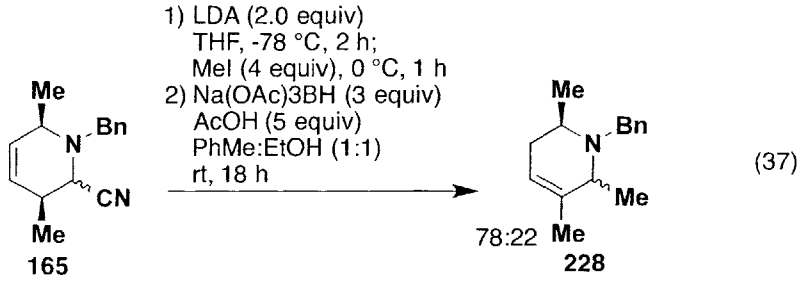
Ellman also reported that the reduction of TMS-substituted piperidines without a substituent at C6 using $NH_4(OAc)_3BH$ proceeded with high diastereoselectivty (Scheme 47).

[93] Girard, N.; Hurvois, J-P.; Toupet, L.; Moinet, C. *Synth. Commun.* **2005**, 711-723.

Scheme 47



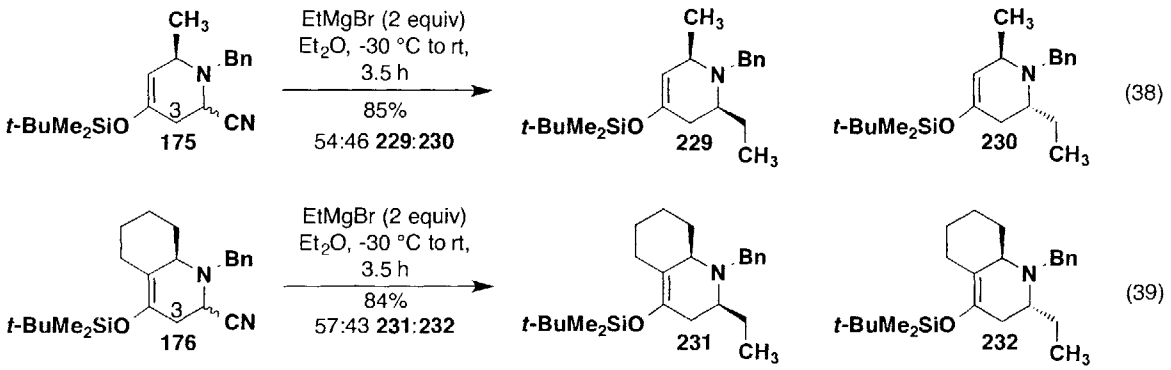
We found that using the same reaction conditions with α-amino nitrile **164** resulted in migration of the double bond and led to formation of a ca. 78:22 mixture of diastereomers of **228** (eq 37). The optimized conditions for reductive decyanation of our cycloadducts continue to be either $NaBH_3CN$/AcOH or Na/NH_3.



(37)

Transformations of Silyl Enol Ether Cycloadducts

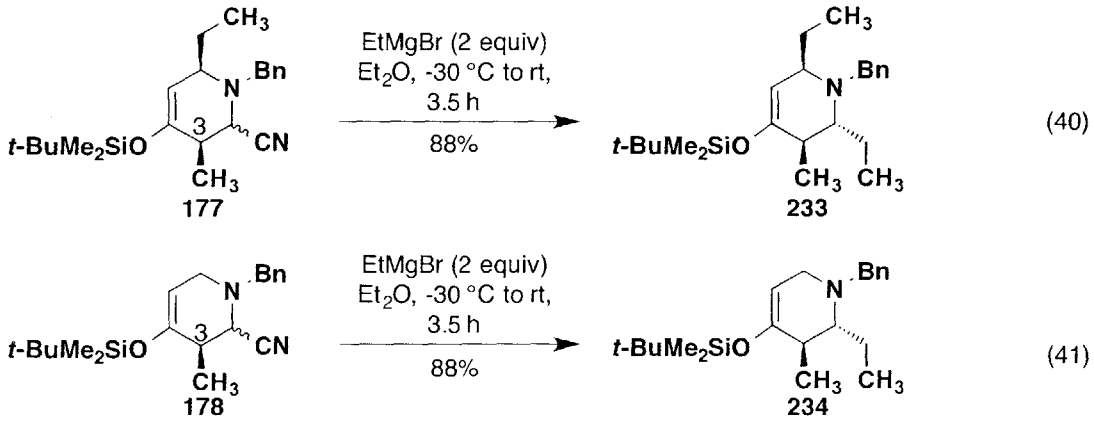
The silyl enol ether cycloadducts (**175**, **176**, **177**, and **178**) participate in Bruylants reactions with yields and diastereoselectivity similar to that of the reactions discussed previously in this chapter. When the substituent at C3 is hydrogen, very poor diastereoselectivity is observed as shown in eq 38 and eq 39. In both cases only a slight preference for the 2,6-*cis* products is observed.



(38)

(39)

On the other hand, when a methyl group is present at C3, we observe high diastereoselectivity for the Bruylants reaction and only the 2,6-*trans* tetrahydropyridines (**233** and **234**) are observed (eq 40 and 41).



(40)

(41)

These structures were assigned by comparison to other tetrahydropyridine products we had already identified. For substrates with C3 alkyl substituents, the nucleophile once again adds to the iminium ion from the face opposite to that substituent. ^{13}C NMR spectroscopy provides evidence in support of the assigned structures. Due to the γ-effect[84], the benzyl carbon is shifted upfield for the 2,6-*trans* products (**235**) since a substituent on the ring is forced into the axial position at the γ-carbon, shielding the benzyl carbon (Figure 15).

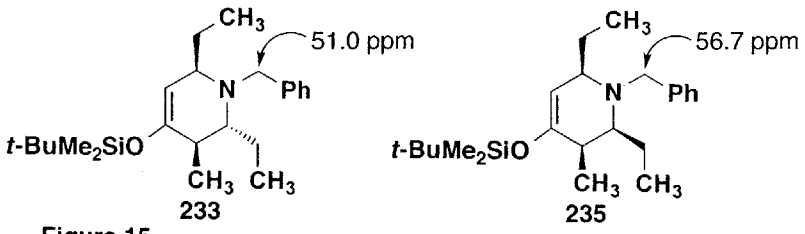
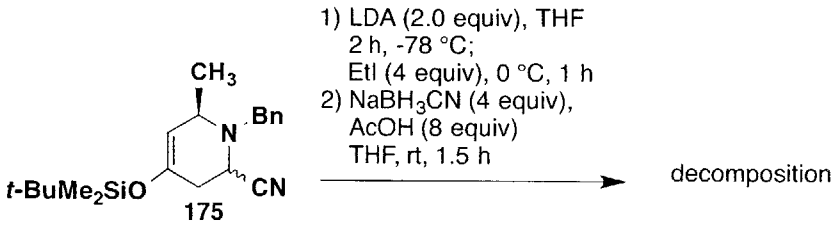


Figure 15

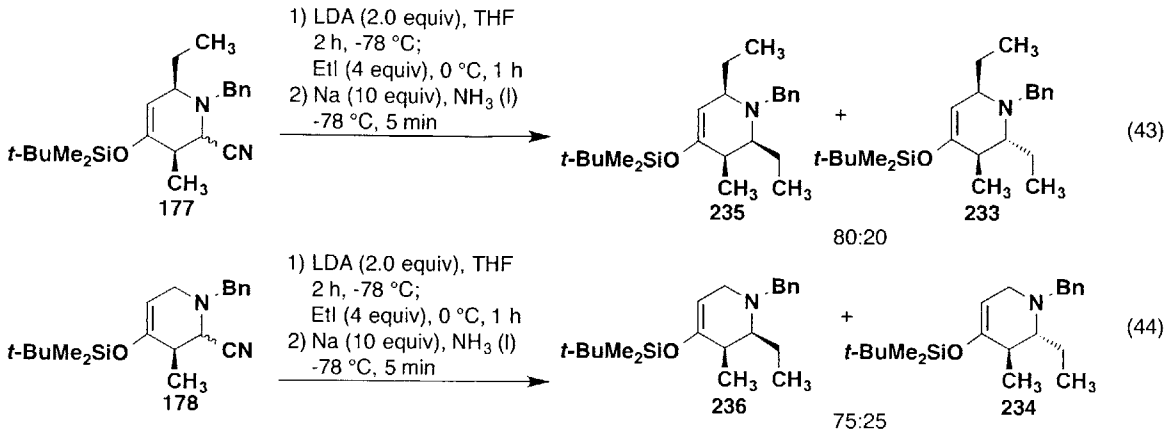
For reductive decyanation of the silyl enol ether cycloadducts, it was found that it is important to use dissolving metal conditions in order to preserve the silyl enol ether moiety. Initially we tried using $NaBH_3CN$/AcOH for the reductive decyanation, but the silyl enol ether was observed to react under these acidic conditions (eq 42).



(42)

Eq 43 shows the reaction of cycloadduct **177** under the optimized alkylation and dissolving metal conditions[94] to afford an 80:20 mixture of **235** and **233**. Similar ratios of diastereomers were observed in the synthesis of **236** and **234** shown in eq 44. The yields for both reactions were not determined because the products were contaminated with small amounts of BHT from the diethyl ether used in the workup. The estimated yield for **235** and **233** was 60% and ca. 80% puritiy. The reactivity of **177** and **178** was similar to that of cycloadduct **165**, and we obtained a similar ratio of diastereomers as expected for substrates with an alkyl substituent at C3.

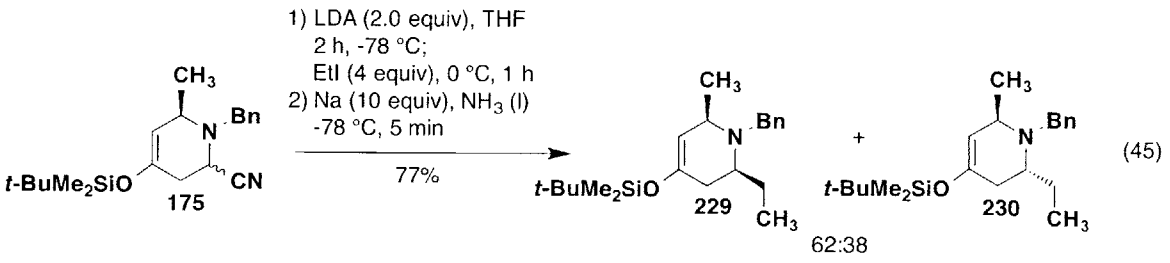
[94] Stirring in Na/NH_3 for an extended period of time results in reduction of the aromatic ring.



(43)

(44)

When an alkyl substituent at C3 is not present, poor diastereoselectivity is observed. Eq 45 shows that metalation of cycloadduct **175** with LDA followed by alkylation and dissolving metal reductive decyanation affords a 62:38 mixture of **229** and **230** in 77% yield. The stereochemical assignment was made based on the chemical shift of the benzylic protons. The benzylic protons for tetrahydropyridine **230** appear as two apparent doublets ($\Delta\nu/J$ = 11.3) and for **229** appear as an AB quartet ($\Delta\nu/J$ = 2.3). As mentioned earlier, the benzyl protons are in a more equivalent environment in the 2,6-*cis* piperidine resulting in a smaller $\Delta\nu/J$ value.



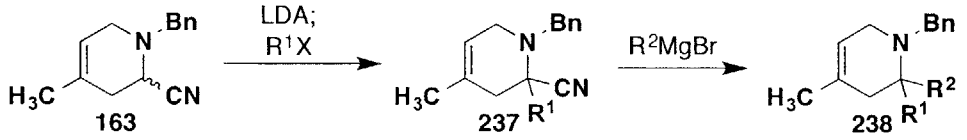
(45)

Quaternary Centers

One of the attractive features of our method is the ability to access a variety of quaternary centers[48f-h] adjacent to the nitrogen in the cycloadducts. Previously David Amos[39] described the formation of quaternary centers by alkylation of quinolizidine cycloadducts followed by

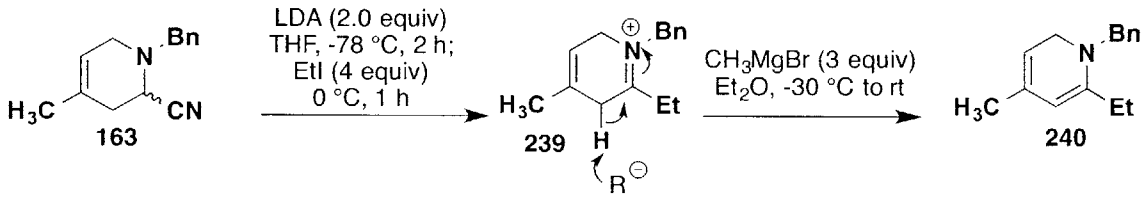
Bruylants reaction on the tertiary amino nitrile product. We were interested in determining whether this approach could be applied to the creation of quaternary centers in our tetrahydropyridine cycloadducts. The strategy proposed is outlined Scheme 48.

Scheme 48



The first set of conditions attempted for this particular transformation are shown in Scheme 49 and was based on the procedure previously optimized by Amos for the elaboration of quinolizidines cycloadducts. Unfortunately, under these conditions the desired product was not produced and the major result was formation of dienamine **240**. Apparently deprotonation of the intermediate iminium ion **239** by the Grignard reagent occurs at a faster rate than 1,2-addition in this case due to increased steric demand in the transition state for addition. As a result, we decided to look at less basic nucleophiles for this study.

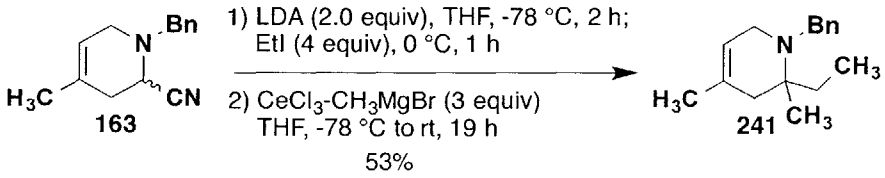
Scheme 49



Organocerium reagents[95] are often used for additions to enolizable ketones. These reagents are less basic than organomagnesium compounds, but still exhibit high nucleophilicity in additions to carbonyl and related functional groups. The organocerium reagents we employed

[95] For reviews on the chemistry of organocerium reagents, see: (a) Liu, H-J.; Shia, K-S.; Shang, X.; Zhu, B-Y. *Tetrahedron* **1999**, *55*, 3803-3830. (b) Bartoli, G.; Marcantoni, E.; Marcolini, M.; Sambri, L. *Chem. Rev.* **2010**, *110*, 6104-6143.

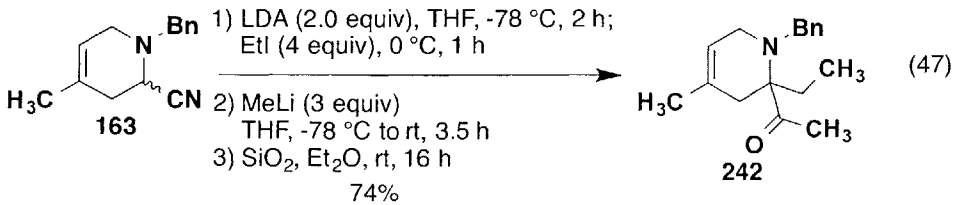
in this study were prepared by first drying $CeCl_3 \cdot 7H_2O$[96] and then adding the desired Grignard reagent at -78 °C. Eq 46 shows the preparation of piperidine **241** possessing a quaternary center. First, the ethyl substituent was installed by alkylation of the α-amino nitrile cycloadduct **163**. In a second pot we then introduced the alkylated product to the pre-formed organocerium reagent in order to install the methyl substituent and furnish **241** in moderate yield over two steps. In this reaction, unreacted tertiary nitrile was isolated even after 19 h.



(46)

During our studies of organocerium reagents, we noticed that it is important to generate the organocerium compound from the corresponding Grignard reagent. Generating the organocerium compound from methyllithium resulted in 1,2-addition to the nitrile rather than 1,2-addition to the iminium ion. It is well known that organocerium reagents have different reactivities depending on the reagents they are prepared from.

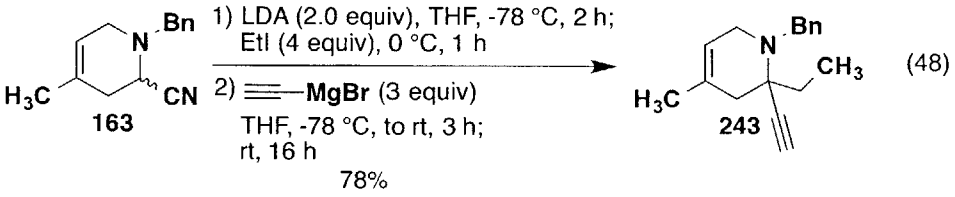
Eq 47 shows the generation of tetrahydropyridine **242** in 74% yield over two steps using methyllithium addition to the nitrile followed by hydrolysis of the resultant imine in a three-pot process.



(47)

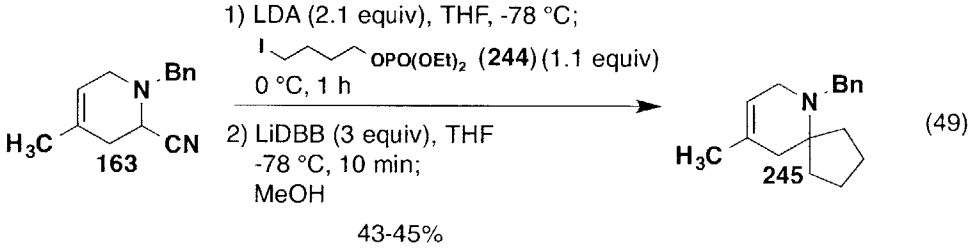
[96] $CeCl_3 \cdot 7H_2O$ was dried under vacuum (13.3 Pa) at 70 °C for 2 h, 100 °C for 3 h, and then 140 °C overnight or lower yields are observed.

Another nucleophile with low basicity we became interested in was ethynylmagnesium bromide. Reaction of the α-amino nitrile **163** with this acetylenic Grignard reagent afforded tetrahydropyridine **243** in 78% yield over two steps.



(48)

The final compound with a quaternary center we synthesized from the isoprene cycloadduct **163** was a molecule with a spiro-fused ring system. Following a procedure similar to that reported by Rychnovsky, cycloadduct **163** was alkylated with phosphoric acid diethyl ester 4-iodo-butyl ester **244**.[97] After reductive lithiation with LiDBB, the phosphate group acted as a good leaving group to yield the desired spirocenter product **245** in moderate yield over two steps.



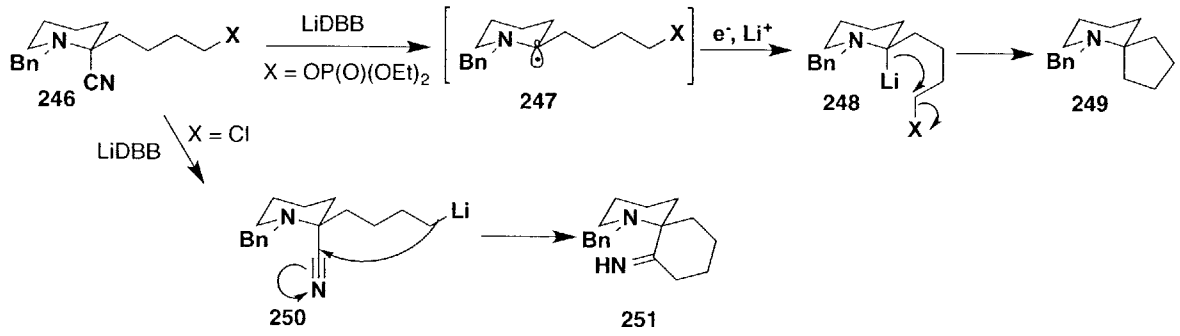
(49)

The phosphate rather than a halide as a leaving group proved to be crucial for the success of the desired cyclization. Initially we employed commercially available 1-chloro-4-iodobutane as the alkylating agent in place of **244**. However, exposure of the alkylation product **246** (X =

[97] For the synthesis of phosphoric acid diethyl ester 4-iodo-butyl ester and generation of a spirocenter, see: Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745-2748.

Cl) to LiDBB reductively lithiated the alkyl chloride, providing **250**, which quickly participated in 1,2-addition to the nitrile to furnish **251** as the final product (Scheme 50).[98]

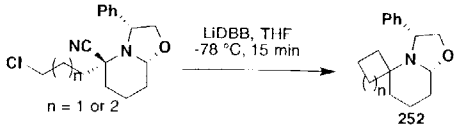
Scheme 50



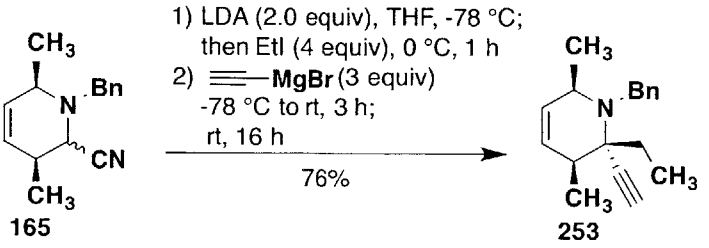
The previous examples demonstrate a wide range of quaternary centers that can be accessed from the α-amino nitrile cycloadducts. Although we have shown that the quaternary centers can be generated in good to excellent yield over two steps, reactions of cycloadduct **163** derived from isoprene do not provide any information on the diastereoselectivity of the reactions. We next turned our attention to reactions of cycloadduct **165** to demonstrate the diastereoselective formation of quaternary centers from our cycloadducts.

Using the same conditions as described in eq 48, we were able to generate piperidine **253** in 76% yield as a single isomer (eq 50). Only the diastereomer **253** was observed in the crude reaction product. Unfortunately, the stereochemistry of the quaternary center was difficult to determine using NMR analysis since the protons of importance are too far apart for NOE enhancement. The stereochemistry shown in **253** is based on the assumption that the

[98] Surprisingly, Husson and coworkers observed spirocenter formation from 1-bromo-4-chlorobutane and no imine formation. Ribeiro, C. M. R.; de Melo, S. J.; Bonin, M.; Quirion, J-C.; Husson, H-P. *Tetrahedron Lett.* **1994**, *35*, 7227-7230.



nucleophilic acetylide adds to the iminium ion from the less sterically hindered face of the ring as was observed in the case of mono-alkylated products studied previously.



(50)

The lowest energy conformation of **253** (Figure 14) was calculated using a HF/6-31G* basis set. The dihedral angles between the proton at C3 and the carbons of each substituent were found to be 48° and 70°. The dihedral angles shown in Figure 14 predict that a smaller ^3J coupling should be present between the proton and the carbon of the ethyl substituent since 70° is closer to the minimum in the ^3J Karplus diagram. The HMBC spectrum, which shows multiple bond couplings between carbons and protons, has a strong cross peak between this proton and the alkyne carbon, strong evidence that this is in fact the correct structure. To further prove the stereochemical assignment, the compounds resulting from addition of a methyl or ethyl nucleophile were synthesized since these were expected to show an NOE between protons on the ring and substituents.

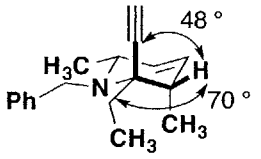
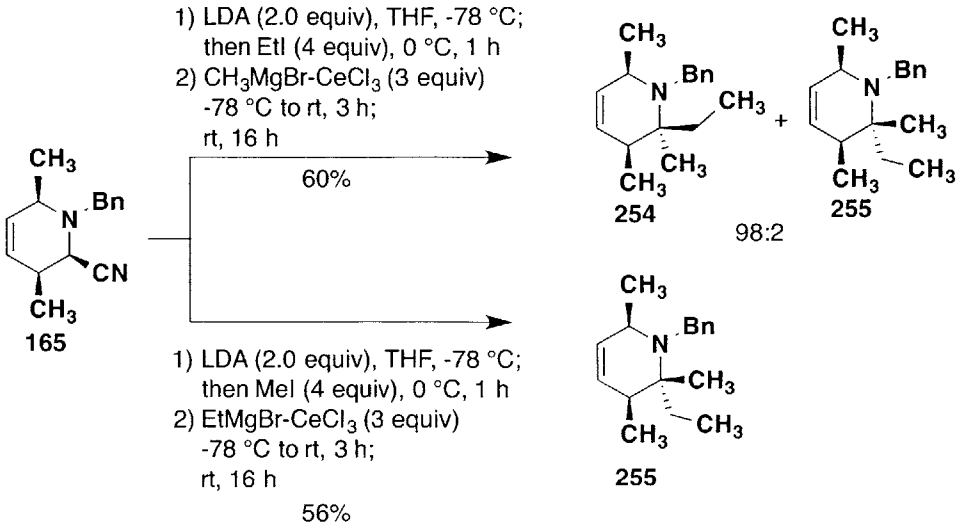


Figure 16

The synthesis of both **254** and **255** using the organocerium chemistry discussed above worked well and provided each product with high diastereoselectivity (Scheme 51)

Scheme 51



Initially, we tentatively assigned the stereochemistry to these products based on the nucleophile adding from the less sterically congested side of the ring. To prove the structure and support our prediction, we performed an "NOE difference" NMR experiment on **255**. Between the proton at C6 and a proton of the methylene on the ethyl group, a 3.8%[99] enhancement was observed (Figure 15). This NOE enhancement not only supports the structures of compounds **253-255**, but also the structures for other substrates with substituents at C3. We were not able to irradiate the methyl group of the quaternary center due to similar shifts to the other methyl substituents.

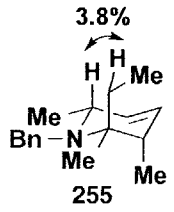


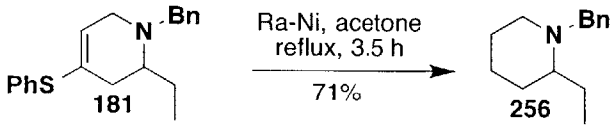
Figure 17. NOE diff

Vinyl Sulfide Reduction

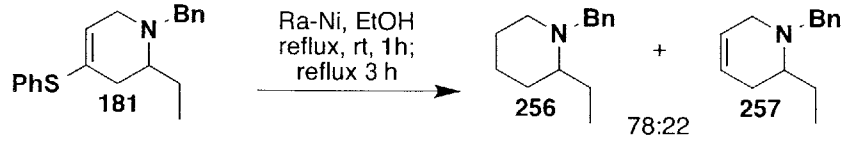
The final transformation we wanted to perform with our tetrahydropyridines involved cleavage of the vinyl sulfide group in cycloadduct **181**. Our aim in preparing vinyl sulfides was

[99] NOE enhancements of 2-5% are indicators of close proximity in molecules.

to identify a group that could be easily cleaved in one step, and that would also act as a good directing group in the [4 + 2] cycloaddition. The most common method for reductively cleaving a vinyl sulfide employs Raney nickel.[100] Stirring **181** over Raney nickel in refluxing acetone afforded *N*-benzyl-2-ethylpiperidine **256** in 71% yield. Switching the solvent to ethanol resulted in a 78:22 mixture of **256** and the tetrahydropyridine **257** in which only the C-S bond had been cleaved.



(51)



(52)

Summary

In summary, the α-amino nitrile cycloadducts generated using our method are exceptional synthetic intermediates. Transformations of cycloadducts with a C3 alkyl substituent proceed with excellent diastereoselectivity. We are also able to install many different quaternary centers, as well as to reduce the vinyl sulfide group to the fully saturated piperidine ring. One limitation to this method is the poor diastereoselectivity for transformations where there is no alkyl substituent present at C3.

[100] For reviews on Raney nickel, see: (a) Hauptmann, H.; Walter, W. F. *Chem. Rev.* **1961**, *62*, 347-404. (b) Smith, A. J.; Trimm, D. L. *Annu. Rev. Mater. Res.* **2005**, *35*, 127-142. (c) Bakker, M. L.; Young, D. J.; Wainwright, M. S. *J. Mater. Sci.* **1988**, *23*, 3921-3926. (d) Augustine, R. L. *Catalytic Hydrogenation: Techniques and Applications in Organic Synthesis*; Marcel Dekker, Inc: New York, 1965. (e) Pizey, J. S. Raney Nickel. *Synthetic Reagents*; John Wiley & Sons Inc: New York, NY, 1974; Vol. 2, pp 175-354.

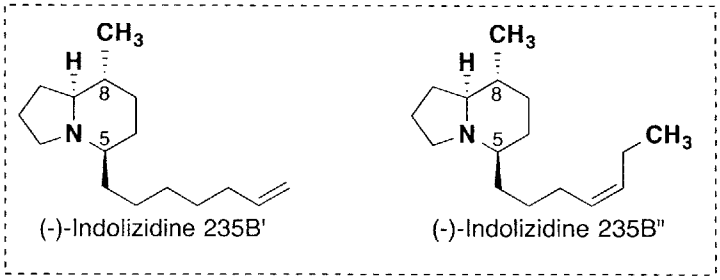
Part III

Intramolecular Aza Diels-Alder Reactions of Iminoacetonitriles: The Total Syntheses of Indolizidines 235B' and 235B"

Chapter 1

Introduction and Background

As discussed in Part I, the intramolecular cycloadditions of iminoacetonitriles can provide efficient access to various bicyclic systems including indolizidines and quinolizidines. A 3-carbon tether between the iminoacetonitrile and diene furnishes, after cycloaddition, an indolizidine that is a backbone of many natural products. Part III describes the synthesis of two natural products, indolizidines 235B' and 235B", that have been isolated from poison dart frogs of Central and South America.



Bioactivity of 8-Methyl-5-substituted Indolizidines

Both indolizidine 235B'[101] and 235B"[102] are members of the 5,8-disubstituted class of indolizidine alkaloids. 8-Methyl-5-substituted indolizidines[103, 104, 105] are non-competitive

[101] For the isolation of 235B', see: Edwards, M. W.; Daly, J. W. *J. Nat. Prod.* **1988**, *51*, 1188-1197.
[102] For the isolation of 235B", see: Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643-652.
[103] For a review of the chemistry and biology of indolizidine and quinolizidine natural products, see: Daly, J. W.; Garraffo, H. M.; Spande, T. F. *In Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: new York, 1999; Vol. 13, pp 1-161.
[104] For a listing and discussion of over 800 natural products isolated from amphibian skin, see: Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575.
[105] For reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139-165. (b) Michael, J. P. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 55, pp 91-258. (c) Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, pp 189-250. (d) Daly, J. W.; Garraffo, M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 43, pp 186-281.

blockers of the nicotinic acetylcholine receptor-channels,[106] and are isolated in minute quantities from poison dart frogs from the family Dendrobatidae.

In 1991, Daly and coworkers reported the bioactivity of many 5,8-disubstituted indolizidines.[106a] Both 235B' and 235B" were included in this study and proved to be significant blockers of carbamylcholine-elicited $^{22}Na+$ influx in PC12 cells.

In a more recent paper, indolizidine 235B' was reported to inhibit nicotinic acetylcholine receptors.[106b] Tsuneki and coworkers discovered that (-)-235B' was selective for α4β2 receptors over several other nicotinic receptors. Tsuneki also describes in detail the selectivity of indolizidine (-)-235B' for acting as an open channel blocker of α4β2 nΛChR receptors.[106b] Mutations in α4 and β2 units are linked to frontal lobe epilepsy so discovering a selective antagonist for specific receptors is a potential treatment for such neurological disorders.

There continues to be importance in exploring the bioactivity of these indolizidine alkaloids, and in 2011 another paper detailed the potential for indolizidine 235B' to inhibit nicotine-evoked [^{3}H]dopamine release.[106d] This suggested a possibility for using indolizidines with similar scaffolds for therapies used to treat smoking addictions.

There are a number of indolizidine alkaloids in this family that have similar structures to indolizidines 235B' and 235B" (Figure 18). These alkaloid natural products are excellent synthetic targets due to their bioactivity and potential applications in the treatment of cholinergic disorders such as Alzheimer's disease. Our aim has been to develop an efficient strategy that

[106] For studies of the bioactivity of 8-methyl-5-substituted indolizidines, see: (a) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1213-1218. (b) Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004**, *66*, 1061-1069. (c) Toyooka, N.; Tsuneki, H.; Kobayashi, S.; Dejun, Z.; Kawasaki, M.; Kimura, I.; Sasaoka, T.; Nemoto, H. *Curr. Chem. Biol.* **2007**, *1*, 97-114. (d) Pivavarchyk, M.; Smith, A. M.; Zhang, Z.; Zhou, D.; Wang, X.; Toyooka, N.; Tsuneki, H.; Sasaoka, T.; McIntosh, J. M.; Crooks, P. A.; Dwoskin, L. P. *Eur. J. Pharmacol.* **2011**, *658*, 132-139.

would have the potential to provide access to the entire family of 8-methyl-5-substituted indolizidine alkaloids. Toward that end we have developed syntheses of indolizidines 235B' and 235B" by an approach that in principal should be applicable to diverse members of this family of natural products.

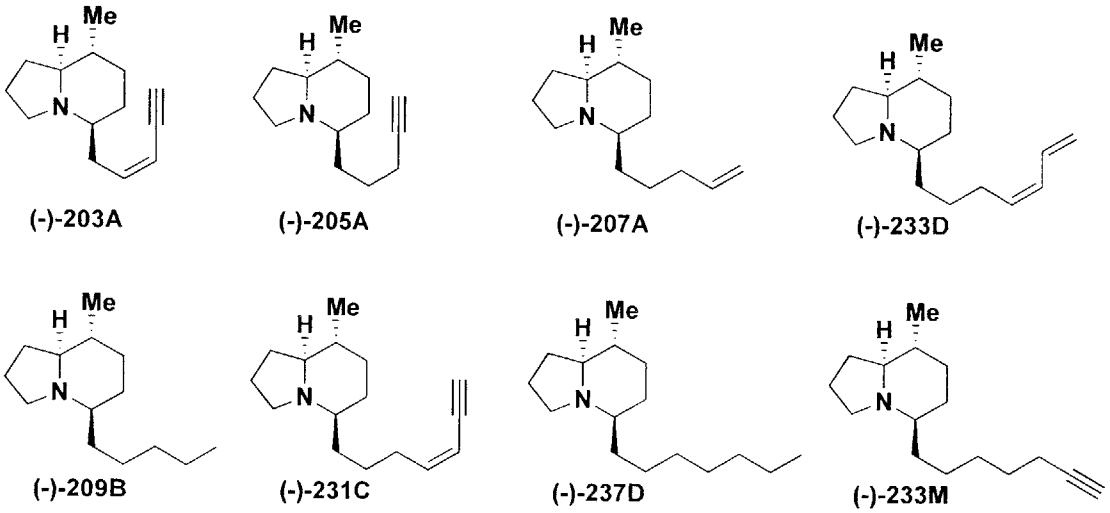


Figure 18. 8-Methyl-5-substituted Indolizidines

Absolute Configuration of Indolizidine 235B"

It is well established that indolizidine (-)-235B' occurs in nature as the levorotatory enantiomer with 5*R*, 8*R*, 9*S* absolute stereochemistry shown above. However, there is some disagreement in the literature over which enantiomer of 235B" is naturally occurring.

In 1987, Daly and Tokuyama reported the isolation of indolizidine 235B", indicating the optical rotation of the natural product to be $[\alpha]_D$ +11.3(*c* 1.0, $CHCl_3$) and assigning it as having

the 5*S*, 8*S*, 9*R* configuration.[102,107] While some total syntheses have been syntheses of racemic alkaloid, others produce (-)-235B", that is, the enantiomer with 5*R*, 8*R*, 9*S* absolute stereochemistry and with rotation *opposite* to that reported by Daly and Tokuyama. The authors of these syntheses suggest that the rotation reported by Daly and Tokuyama was erroneous, based on the fact that all other 8-methyl-5-substituted indolizidine alkaloids isolated from poison dart frogs are levorotatory. Many of these authors suggest that Daly and Tokuyama obtained an erroneous rotation due to impurities in their sample of the natural product.

Toyooka did address this issue in a 2005 publication.[108] In this paper the goal was to determine the absolute stereochemistry of another indolizidine alkaloid, 237D. Alkaloid 237D has the same skeleton as 235B' and 235B" but no unsaturation in the seven-carbon side chain. The paper reports that hydrogenation of samples of natural (+)-235B" and (-)-235B' provide two saturated *enantiomeric* compounds, (+)-237D and (-)-237D (Scheme 52). Gas chromatography using a chiral column showed good baseline separation for the two enantiomers. These experiments appear to confirm that the natural isomer of 235B" is indeed the dextrorotatory isomer (5*S*, 8*S*, 9*R*) in spite of the fact that other indolizidine alkaloids have the opposite configuration at the three substituents.

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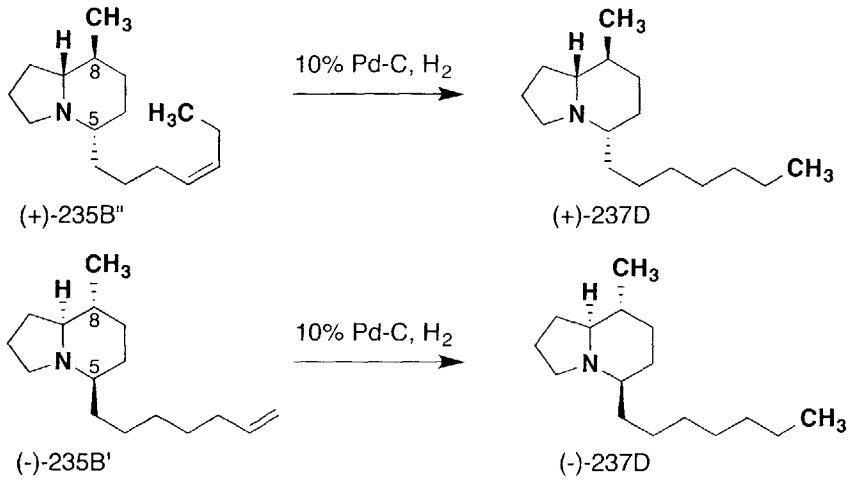
[107] A source of confusion is that the authors initially referred to this compound as indolizidine 235B, but later (see ref. 102) changed the name to 235B".

[108] Toyooka, N.; Kawasaki, M.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M. *Heterocycles* **2005**, *65*, 5-8. Note that the stereochemistry of all structures in the original version of this paper were given incorrectly and were corrected in an erratum (Toyooka, N.; Kawasaki, M.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M. *Heterocycles* **2006**, *68*, 1317).

Scheme 52



We have learned from Professor Toyooka that these hydrogenation experiments were performed at NIH in Dr. Daly's laboratory.[109] It is Professor Toyooka's opinion that the sample of 235B" at NIH was contaminated with a dextrorotatory impurity and that the product of its hydrogenation was not necessarily (+)-237D. Professor Toyooka believes that the absolute configuration of indolizidine alkaloid 235B" is actually 5R, 8R, 9S, and that the pure natural product is therefore actually levorotatory. Unfortunately, Dr. Daly passed away in 2008 and it is not possible to unequivocally establish the identity of the natural material he isolated.

Previous Syntheses of Indolizidines 235B' and 235B"

To date there have been several total syntheses for both indolizidine 235B'[110] and 235B".[111] The following section describes past methods for synthesizing these alkaloids. Many of the strategies reported in the literature are used to synthesize both natural products since their structures only differ by the location of the carbon-carbon double bond in the side chain.

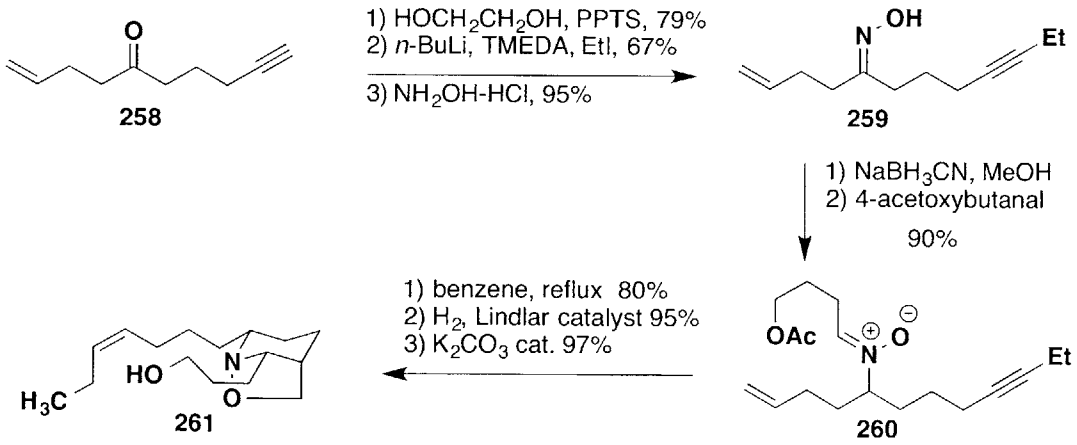
[109] Personal communications, Naoki Toyooka to Rick Danheiser, June, 2013.
[110] To date, 2 unique routes to indolizidine 235B' have been reported.
[111] To date, 7 unique routes to indolizidine 235B" have been reported.

Synthesis via Intramolecular Thermal Cycloaddition of (Z)-N-Alkenylnitrones

In 1991, Holmes and coworkers reported the synthesis of both indolizidines 235B' and 235B" in racemic form via an adaptation of their method for the synthesis of all-*cis* 2,3,6-trisubstituted piperidines.[112] Holmes's synthesis utilized an intramolecular dipolar cycloaddition reaction of a nitrone and furnished racemic 235B" in 18 steps.

Ketone **258** was prepared in three steps from commercially available 3-ethoxy-2-cyclohexenone.[113] Installation of the ethyl group and oxime synthesis required three steps and afforded **259**. Reduction of **259** and condensation with 4-acetoxybutanal furnished nitrone **260** in excellent yield. The dipolar cycloaddition of **260** followed by reduction of the alkyne to the *Z*-olefin and deprotection of the alcohol furnished the bicyclic intermediate **261** in high yield as a single diastereomer. The key cycloaddition step set the relative (all-cis) stereochemistry of the substituents on the piperidine ring.

Scheme 53

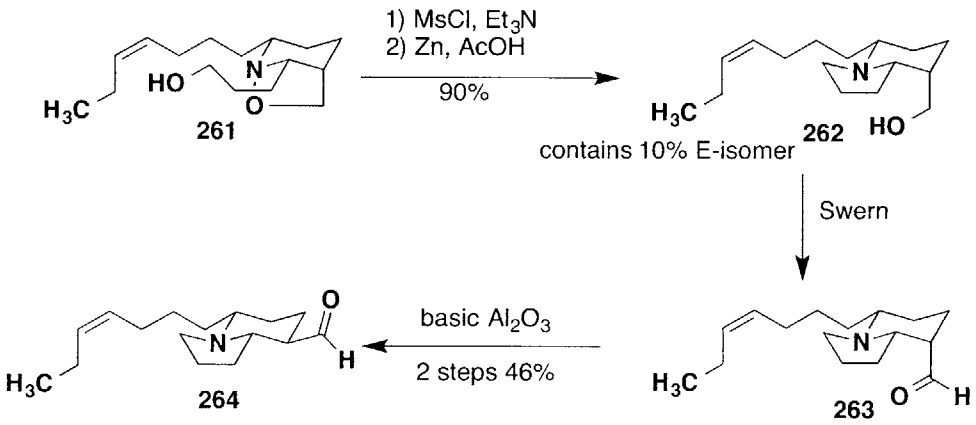


[112] Collins, I.; Fox, M. E.; Holmes, A. B.; Williams, S. F.; Baker, R.; Forbes, I. J.; Thompson, M. *J. Chem. Soc. Perkin Trans. 1.* **1991** 175-182.

[113] For the synthesis of 235B' using this method, hex-5-en-2-one was used as the starting ketone.

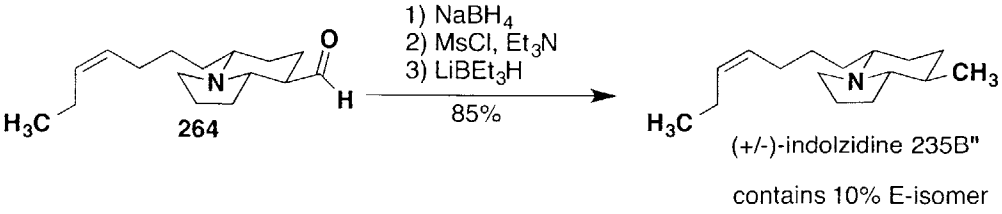
The five-membered ring was next constructed by mesylation of the alcohol and immediate cyclization onto the nitrogen to form an ammonium salt. Exposure to zinc reductively cleaved the N-O bond and furnished indolizidine **262** in excellent yield over two steps (Scheme 54). Holmes reported that some alkene isomerization took place during this sequence and the isomer was carried through the synthesis because it was difficult to separate by chromatography. Swern oxidation of the primary alcohol followed by epimerization to the thermodynamically favored equatorial aldehyde proceeded in moderate yield over two steps to afford **264**.

Scheme 54



The final steps of the synthesis included reduction of the aldehyde to a methyl group over three steps to furnish (±)-indolizidine 235B" in excellent yield. This strategy was also used to prepare (±)-indolizidine 235B' in 14 steps using a different ketone to begin the synthesis.

Scheme 55



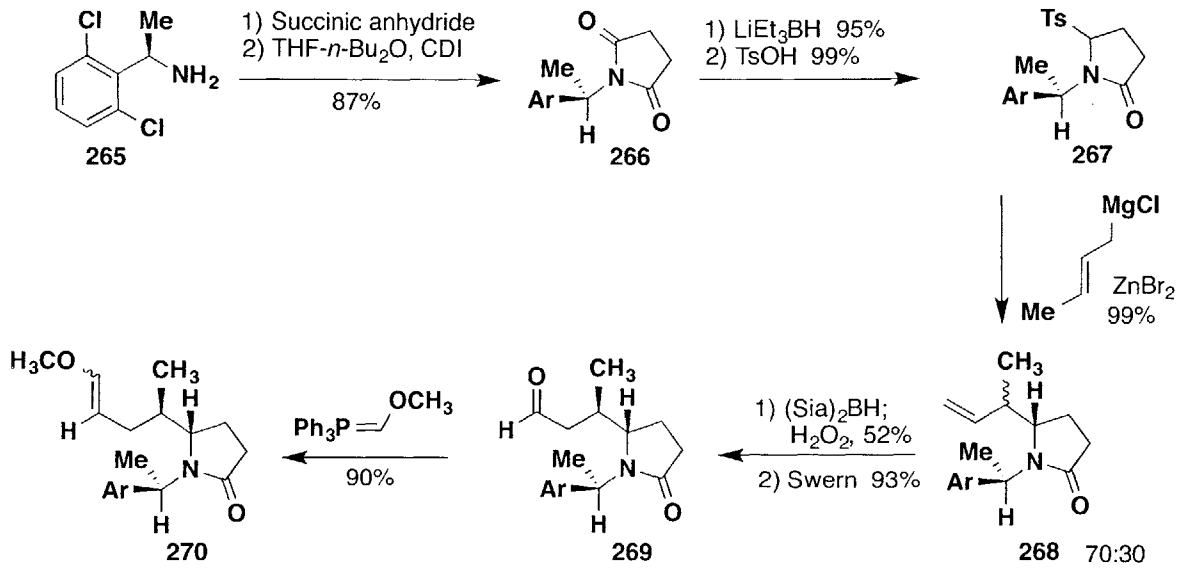
Holmes's strategy for the construction of indolizidine systems via a dipolar cycloaddition of nitrones demonstrates an excellent way to access a variety of the 8-methyl-5-substituted indolizidines in a diastereoselective manner. However, several steps are required to access the nitrone substrate for the cycloaddition, and many functional group manipulations are necessary to complete the synthesis after the key cycloaddition step. Another drawback of this strategy is that it only provides access to racemic alkaloid, which is also contaminated with 10% of the *E*-olefin.

Synthesis via a Chiral Acyliminium Ion

In 1991, Polniaszek and Belmont reported the synthesis of indolizidine (-)-235B" in 13 steps from (*R*)-2,6-dichlorophenylethylamine.[114] Their synthesis proceeded through a late stage α-amino nitrile. The chiral succinimide **266** was prepared from (*R*)-2,6-dichlorophenylethylamine in 87% yield. Reduction of the succinimide with lithium triethylborohydride provided the hydroxy lactam as a 95:5 mixture of diastereomers. The *p*-toluenesulfonyl lactam **267** was synthesized as a single diastereomer without assignment of the stereochemistry. Reaction of the chiral latent acyliminium ion with prochiral crotylmagnesium chloride afforded a 70:30 mixture of stereoisomeric lactams **268** in quantitative yield. In order to separate the two diastereomers, Polniaszek performed hydroboration of the terminal olefin and separated the two primary alcohols by silica gel chromatography. At this stage in the synthesis, the methyl bearing stereocenter of the natural product was set. Swern oxidation of the resulting alcohol and Wittig olefination provided **270** in excellent yield.

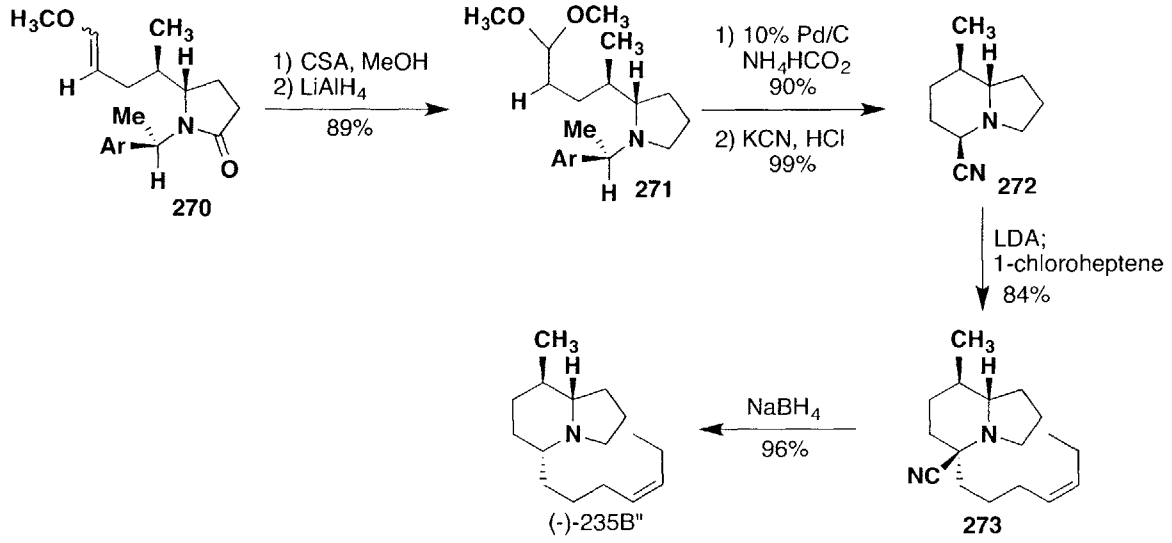
[114] Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868-4874.

Scheme 56



The inseparable mixture of enol ethers was stirred in the presence of camphorsulfonic acid and methanol to furnish the dimethylacetal (Scheme 57). Reduction of the lactam followed by hydrogenolysis of the phenylethyl protecting group set the substrate up for the final cyclization. Hydrolysis of the acetal and cyclization in the presence of HCN afforded α-amino nitrile **272** in excellent yield. The α-amino nitrile was then alkylated with 1-chloroheptene and reductively decyanated with sodium borohydride to afford indolizidine (-)-235B".

Scheme 57



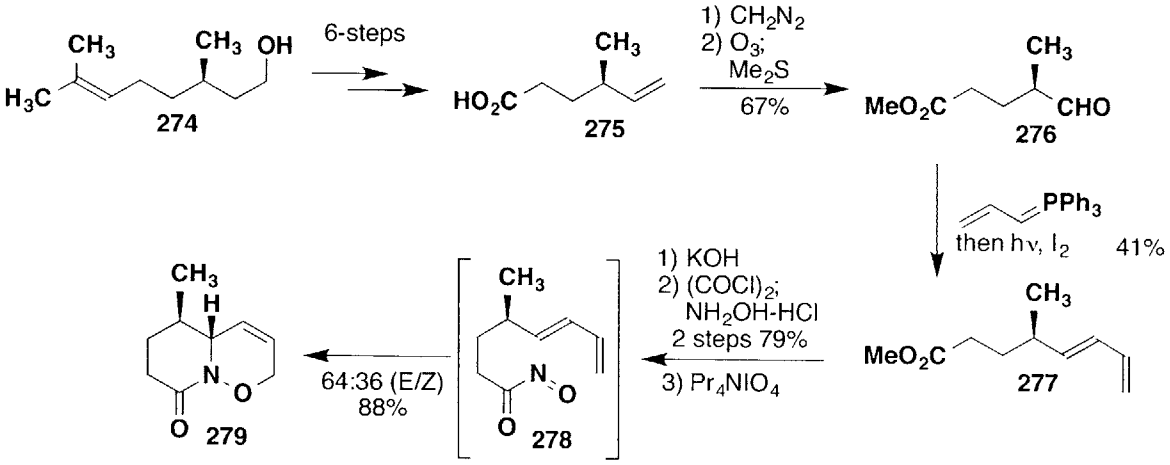
Alkylation of the α-amino nitrile proceeded smoothly. Introduction of the hydride proceeded via axial nucleophilic attack on the iminium ion to furnish indolizidine (-)-235B" in excellent yield as a single diastereomer with the 5*R*, 8*R*, 9*S* configuration. This synthesis illustrates the excellent utility of chiral auxiliaries; however, the crotylmagnesium chloride addition only proceeded with a dr of 70:30.

Polniaszek comments on the difference between the absolute configuration of his synthetic indolizidine and that of the natural isomer. While the ^{1}H and ^{13}C NMR data were identical to that of the natural isomer, the magnitude and sign of the optical rotation was different from the published value for the alkaloid. Polniaszek speculated that an impurity in the natural sample may be responsible for the (+)-rotation and he chose to synthesize the (-)-enantiomer in the belief that the natural product has the 5*R*, 8*R*, 9*S* stereochemistry rather than the 5*S*, 8*S*, 9*R* configuration reported in the isolation paper.

Synthesis via Intramolecular Diels-Alder Reaction of a N-Acylnitroso Dienophile

In 1991, Kibayashi reported a 17-step synthesis of indolizidine (-)-235B" via the intramolecular Diels-Alder reaction of an *N*-acylnitroso compound.[115] Carboxylic acid **275** was prepared in 6 steps from (*R*)-citronellol (**274**). Conversion of **275** to aldehyde **276** via esterification and ozonolysis proceeded in moderate yield over two steps. Wittig olefination of the aldehyde provided an E/Z mixture of dienes, which were converted to the desired *E*-isomer via photoisomerization in 41% yield. Hydrolysis of methyl ester **277** followed by acid chloride formation and reaction with hydroxylamine provided the corresponding oxime, which was the last isolable intermediate before the key step. Oxidation to *N*-acylnitroso **278** followed immediately by [4 + 2] cycloaddition afforded a 64:36 mixture of bicyclic oxazinolactams in 88% yield which were separated by chromatography and recrystallization.

Scheme 58

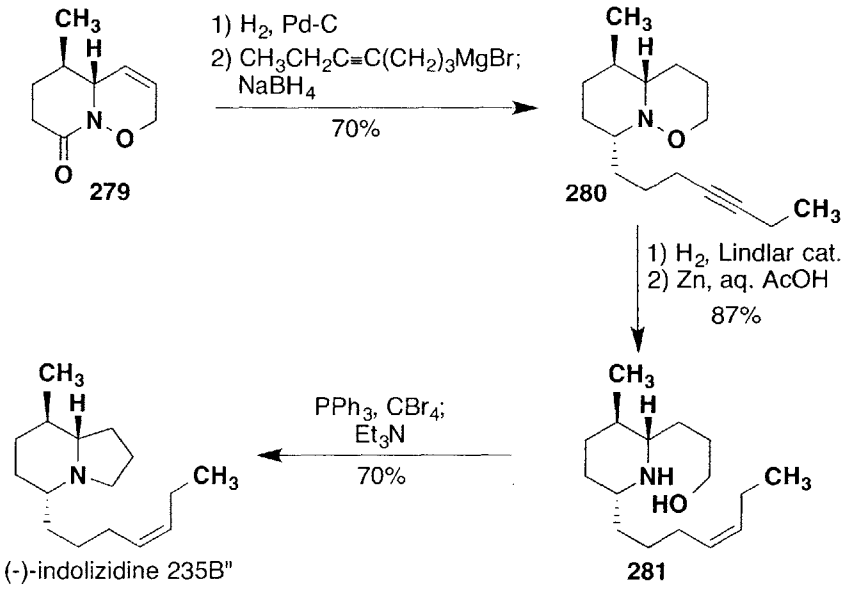


The next task was installation of the heptenyl substituent at C5. Grignard addition to the carbonyl group followed by $NaBH_4$ reduction in a single pot furnished **280** in 70% yield over

[115] (a) Shishido, Y.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1237-1239. (b) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876-2883.

two steps. Axial attack on the iminium ion by hydride set the stereochemistry of the heptenyl group. Reduction of the alkyne to a *Z*-alkene using Lindlar hydrogenation followed by N-O bond cleavage with zinc afforded **281** in 87% yield over 2 steps. The final step in the synthesis was cyclization to form the 5-membered ring of the indolizidine via an Appel reaction.

Scheme 59



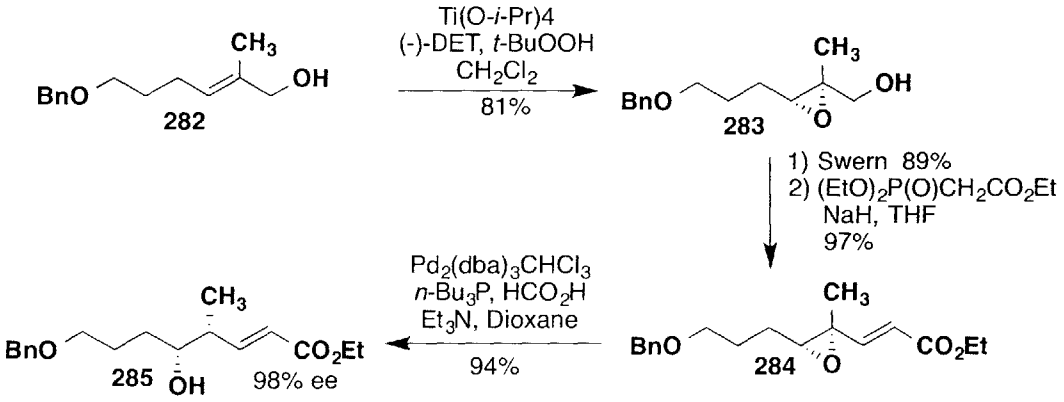
The synthesis reported by Kibayashi demonstrates high diastereoselectivity for the incorporation of the side chain using stereoelectronically controlled hydride addition to an iminium ion. One limitation to this method is the low diastereoselectivity of the cycloaddition (64:36). Fortunately the stereoisomers were separable, but a large portion of cycloadduct had to be discarded.

Kibayashi synthesized indolizidine (-)-235B" with configuration opposite to that reported for the natural product and commented that several other indolizidines isolated from nature are also levorotatory. He attributed the discrepancy in the optical rotation of the natural product sample to a dextrorotatory impurity in the sample.

Synthesis via Palladium-Catalyzed Hydrogenolysis of Alkenyl Oxiranes

In 1993, Satake and Shimizu reported the synthesis of several 8-methyl-5-substituted indolizidines via the common intermediate hexahydro-8-methyl-5-indolizinone.[116] The synthesis started with Sharpless asymmetric epoxidation of **282**. Swern oxidation of the primary alcohol followed by Horner-Wadsworth-Emmons olefination provided **284** in 70% over 2 steps. Hydrogenolysis of the oxirane using a method developed by Shimizu proceeded with high regio- and stereoselectivity to afford alcohol **285** in 94% yield. The desired stereochemistry of the natural product is set during this sequence.

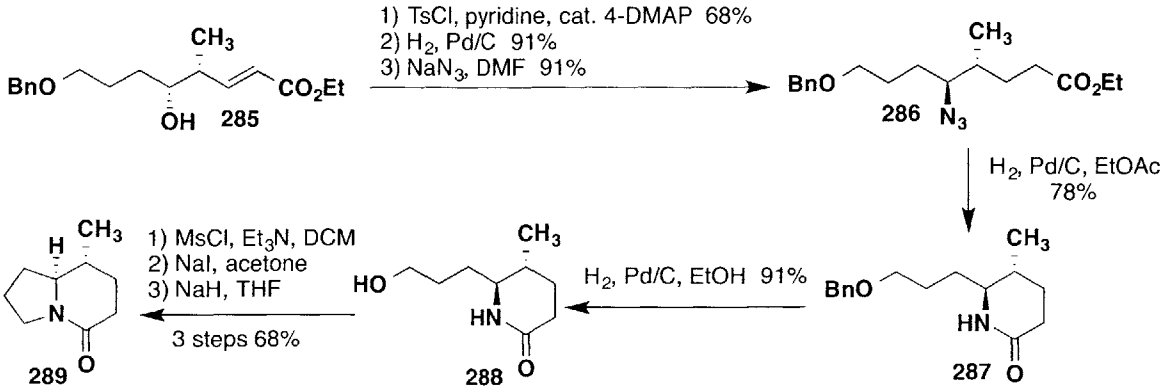
Scheme 60



Formation of the tosylate, followed by azide substitution with inversion of stereochemistry, and hydrogenation of the alkene afforded **286** in a 3 step sequence (Scheme 61). Reduction of the azide and cyclization in one step provided lactam **287** in good yield. Cleavage of the benzyl protecting group via hydrogenolysis in ethanol provided a primary alcohol **288** which was transformed into an alkyl iodide in two steps via a mesylate. The final cyclization was promoted by NaH to afford indolizidinone **289** in excellent yield over 3 steps.

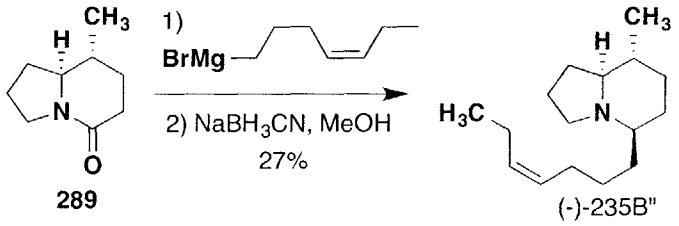
[116] Satake, A.; Shimizu, I. *Tetrahedron: Asymmetry* **1993**, *4*, 1405-1408.

Scheme 61



The final two steps in the synthesis included installing the heptenyl substituent with the correct absolute stereochemistry. 1,2-Addition of the Grignard nucleophile to the carbonyl group of **289** followed by reduction with $NaBH_3CN$ produced indolizidine (-)-235B" in 27% yield.

Scheme 62



Like Kibayashi, Shimizu used stereoelectronic control to set the desired stereochemistry of the substituent. Although the synthesis was completed in 14 steps, the final reaction sequence proceeded in 27% yield, a major drawback to this synthesis.

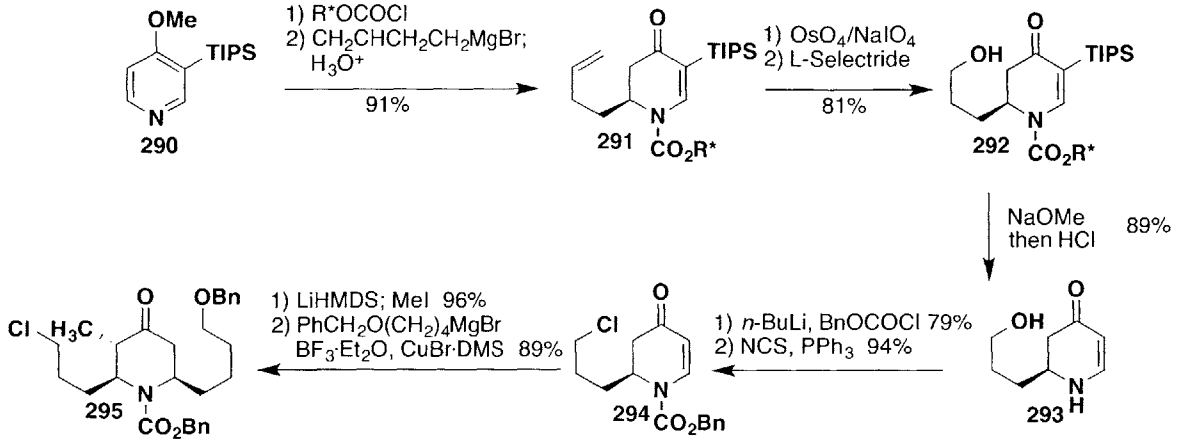
Shimizu synthesized indolizidine 235B" with a (-) optical rotation. He mentions in a footnote the positive rotation of the natural isomer reported by Daly and Tokuyama, but does not comment on the difference and why he chose to synthesize the levorotatory isomer.

Synthesis via 2,3-Dihydro-4-pyridones

Comins and coworkers have reported the use of dihydropyridones as synthetic building blocks for alkaloid synthesis. Comins strategy uses a chiral auxiliary to install substituents on a piperidone ring with high stereoselectivity. In 1997, a synthesis of indolizidine (-)-235B" was reported using this strategy.[117] The synthesis begins with the preparation of a chiral 1-acylpyridinium salt via acylation of the respective pyridine with chiral (+)-*trans*-2-(α-cumyl)cyclohexanol chloroformate. Diastereoselective Grignard addition to the pyridinium salt afforded **291** in 91% yield after recrystallization and chromatographic separation of the 95:5 mixture of diastereomers. Oxidative cleavage of the terminal olefin and reduction to the primary alcohol furnished **292** in 81% yield. Exposure of **292** to sodium methoxide cleaved the chiral auxiliary, and exposure to HCl to facilitate protodesilylation afforded mono-substituted piperidone **293** in 89% yield. Protection of the nitrogen and substitution of the alcohol with chloride set up the piperidone for further stereoselective alkylation. Alkylation of the ring on the less hindered face followed by stereoelectronically controlled Michael addition furnished **295**. The carbon nucleophile added to the enone via axial attack to provide one diastereomer of **295**. Substituents are forced into the axial position due to A(1,3) strain between the alkyl substituent and the *N*-acyl group (Figure 19).

[117] (a) Comins, D. L.; Joseph, S. P.; Hong, H.; Al-awar, R. S.; Foti, C. J.; Zhang, Y.; Chen, Z.; LaMunyon, D. H.; Guerra-Weltzien, M. *Pure Appl. Chem.* **1997**, *69*, 477-481. (b) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182-8187.

Scheme 63



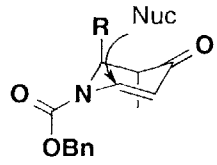
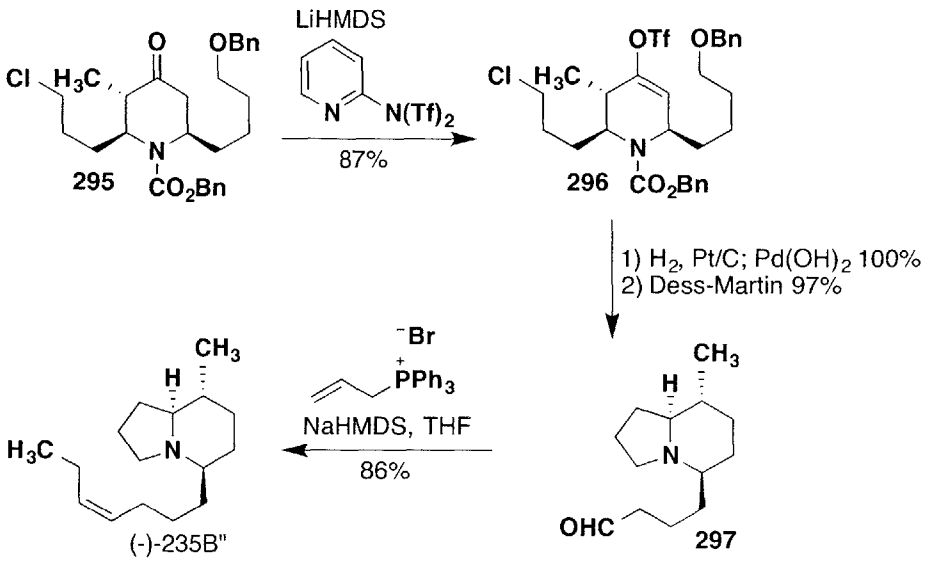


Figure 19

Scheme 64 shows the endgame of the synthesis. After all stereocenters were set on the piperidone, a vinyl triflate was formed. Comins attempted to form the vinyl triflate by trapping after 1,4-addition, but with little success. Hydrogenolysis of the Cbz group immediately resulted in cyclization to form the indolizidine. Hydrogenation using Pt/C and $Pd(OH)_2$ as catalysts reduced the vinyl triflate and effected benzyl ether cleavage of **296**. Oxidation of the primary alcohol to the aldehyde followed by stereoselective Wittig olefination afforded indolizidine (-)-235B" in excellent yield.

Scheme 64



The synthesis reported by Comins involves an elegant stereoselective functionalization of a piperidone. The synthesis is completed in 13 steps from **290** but it does begin with the pyridine **290** which itself requires one step for preparation from 4-methoxypyridine. Many functional group manipulations are involved in this synthesis.

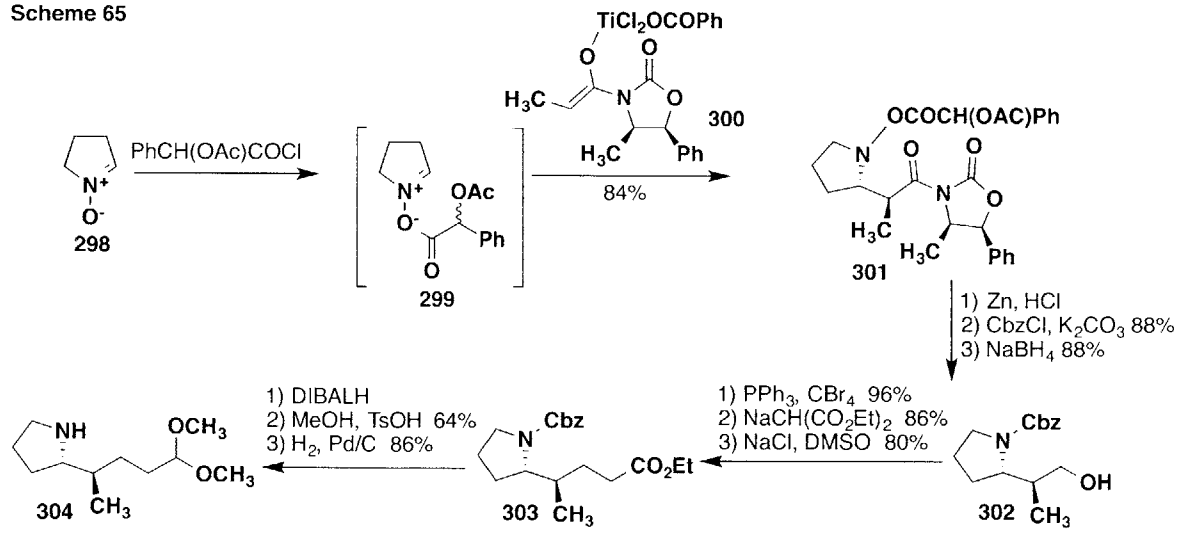
Comins reported that the ^{1}H and ^{13}C NMR data for his synthetic indolizidine (-)-235B" was identical to that of the natural isomer. Comins also mentioned that MS, FTIR, and GC retention times of the synthetic material were compared to the natural isomer and were in agreement. The comparison work was performed by Dr. Thomas Spande at National Institutes of Health. Comins does synthesize the levorotatory isomer with a 5*R*, 8*R*, 9*S* absolution configuration opposite to that of the natural isomer.

Synthesis via Addition to Chiral Enolates to N-Acyloxyiminium Ions

In 1999, Murahashi and coworkers reported a method for the asymmetric synthesis of β-amino acids.[118] Their method involves the addition of chiral enolates to *N*-acyloxyiminium ions and was applied to the formal synthesis of indolizidine (-)-235B". Unlike other total syntheses of indolizidines, in this case the 5-membered nitrogen-containing ring was first manipulated and the 6-membered ring was the result of a cyclization step.

The synthesis started with 1-pyrroline *N*-oxide, prepared from pyrrolidine in one step. *N*-(acetylmandelyloxy)iminium ion **299** was prepared and immediately exposed to titanium enolate **300** to afford **301** in 98:2 dr. N-O bond cleavage using zinc, followed by Cbz protection and reductive cleavage of the chiral oxazolidinone afforded β-amino alcohol derivative **302** in 77% yield. Elongation of the carbon chain over three steps afforded **303** in excellent yield. Reduction of the ester, acetal formation, and deprotection of the amine furnished the substrate ready for cyclization.

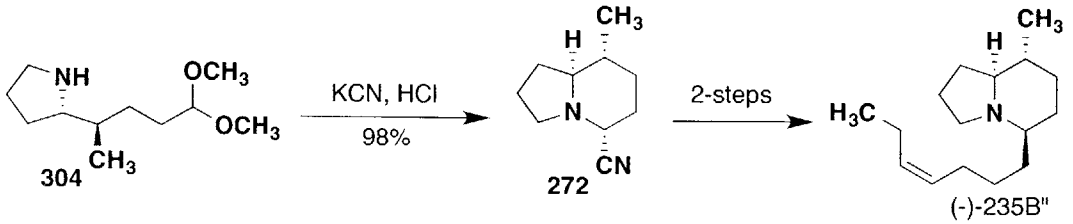
Scheme 65



[118] Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S-I. *Org. Lett.* **1999**, *1*, 107-110.

Stirring amino acetal **304** in the presence of KCN and HCl afforded α-amino nitrile **272** in excellent yield. This completed the formal total synthesis of (-)-235B". There was no mention in the paper of which enantiomer Murahashi believe to be the natural isomer. They simply commented that (-)-235B" could be synthesized from **272** using the methods reported by Polniaszek.[114]

Scheme 66

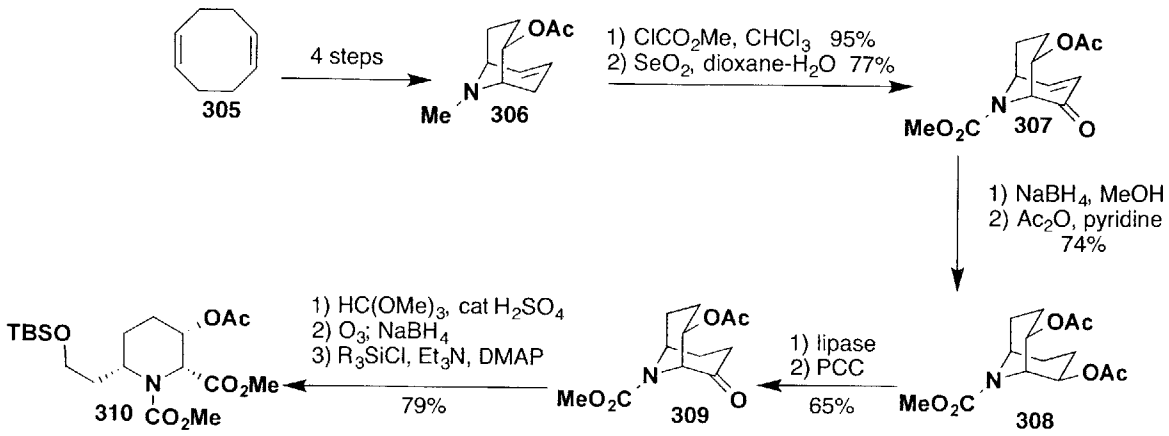


Synthesis via a Chiral Piperidine

In 1997, Toyooka and coworkers synthesized indolizidine (-)-235B' via a chiral piperidine in 28 steps.[119] The synthesis proceeded through diacetate **308**, which was prepared in 8 steps from 1,5-cyclooctadiene. Selective lipase hydrolysis of the acetate followed by PCC oxidation provided **309** in 65% yield over two steps as a single enantiomer. Formation of an enol ether followed by ozonolysis and protection of the resulting alcohol proceeded in 79% yield over three steps.

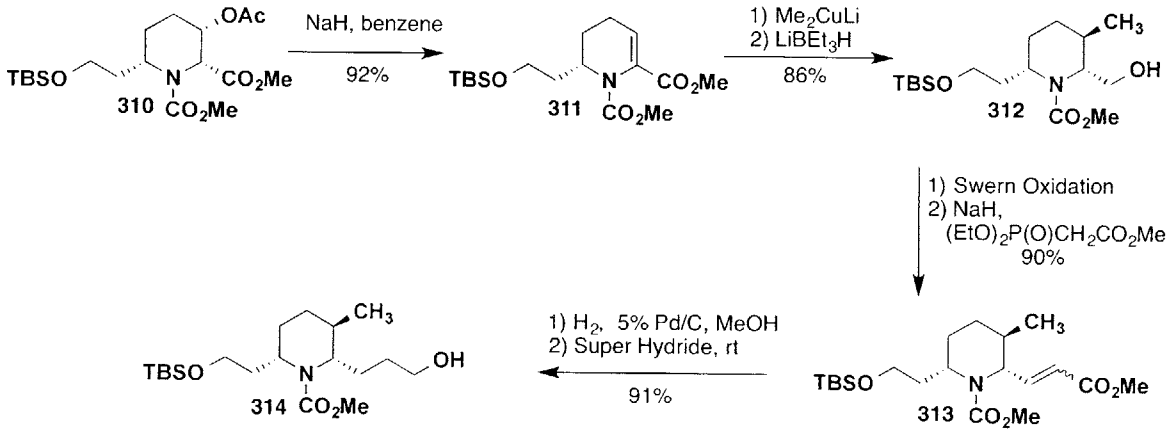
[119] (a) Toyooka, N.; Tanaka, K.; Momose, T.; Daly, J. W.; Garraffo, H. M. *Tetrahedron* **1997**, *53*, 9553-9574. (b) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943-945. (c) Momose, T.; Toyooka, N.; Jin, M. *Tetrahedron Lett.* **1992**, *33*, 5389-5390.

Scheme 67



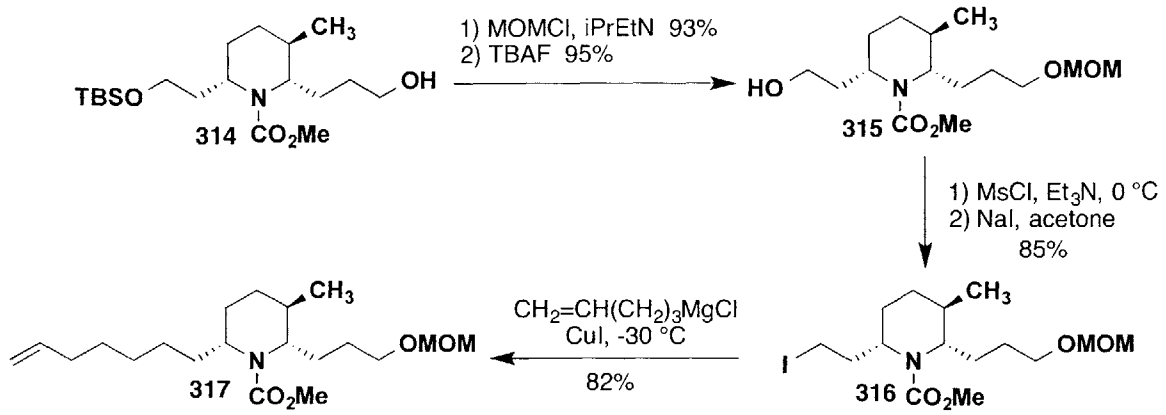
With the enantiopure piperidine in hand, elimination of the acetate provided the unsaturated ester **311,** which underwent diastereoselective methylcuprate addition via axial attack (Scheme 68). The siloxyethyl substituent is forced into the axial position due to A(1,3) strain with the protecting group on nitrogen. Carbon extension of the side chain was accomplished in five steps to afford **314** in high yield.

Scheme 68



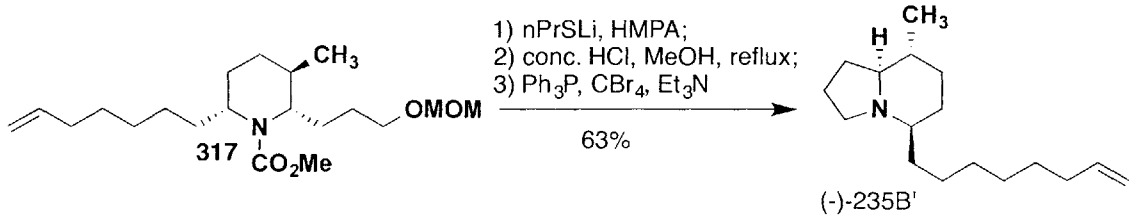
After several functional group manipulations, the heptenyl substituent of the natural product was installed (Scheme 69). The synthesis of other natural products can be achieved by the incorporation of a different substituent at this stage in the synthesis.

Scheme 69



Finally, the indolizidine was constructed via a cyclization strategy. Deprotection of the amine and MOM ether over two steps afforded the appropriate substrate for an Appel reaction and cyclization (Scheme 70). The synthesis does illustrate a stereoselective strategy, but 28 steps does not make it an efficient synthesis capable of generating significant quantities of natural product.

Scheme 70



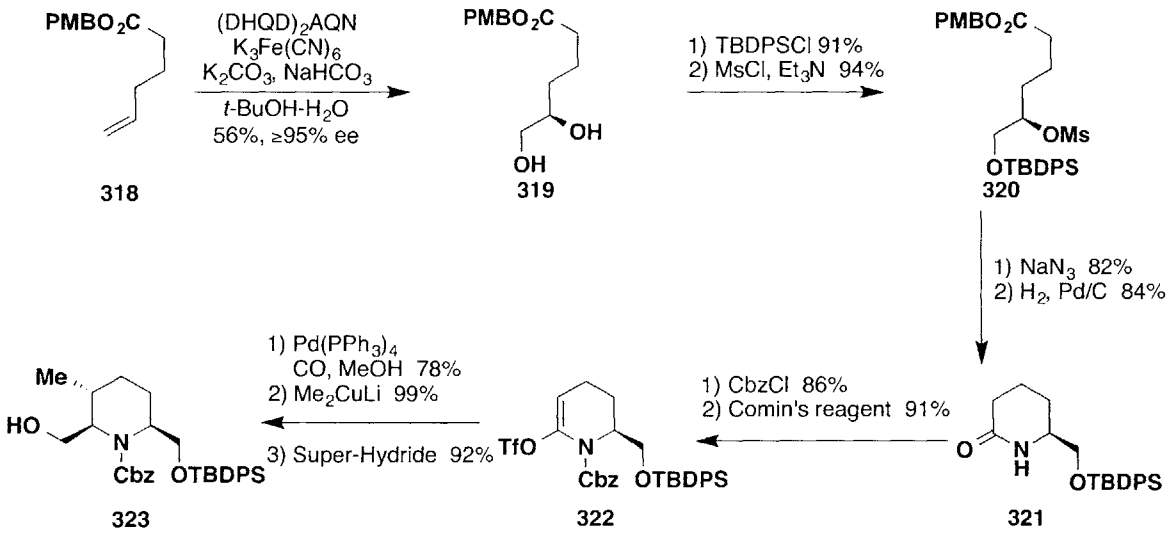
Synthesis via a Chiral Piperidone

In 2006, Toyooka and coworkers reported a synthesis of indolizidine (-)-235B" via enantiomerically pure piperidone **321** (synthesized in five steps from alkenyl ester **318**).[120] Protection of the nitrogen atom and treatment of the piperidone with LiHMDS and Comins' reagent provided vinyl triflate **322**. Palladium catalyzed carbonylation followed by cuprate 1,4-

[120] Toyooka, N.; Dejun, Z.; Nemoto, H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron Lett.* **2006**, *47*, 577-580.

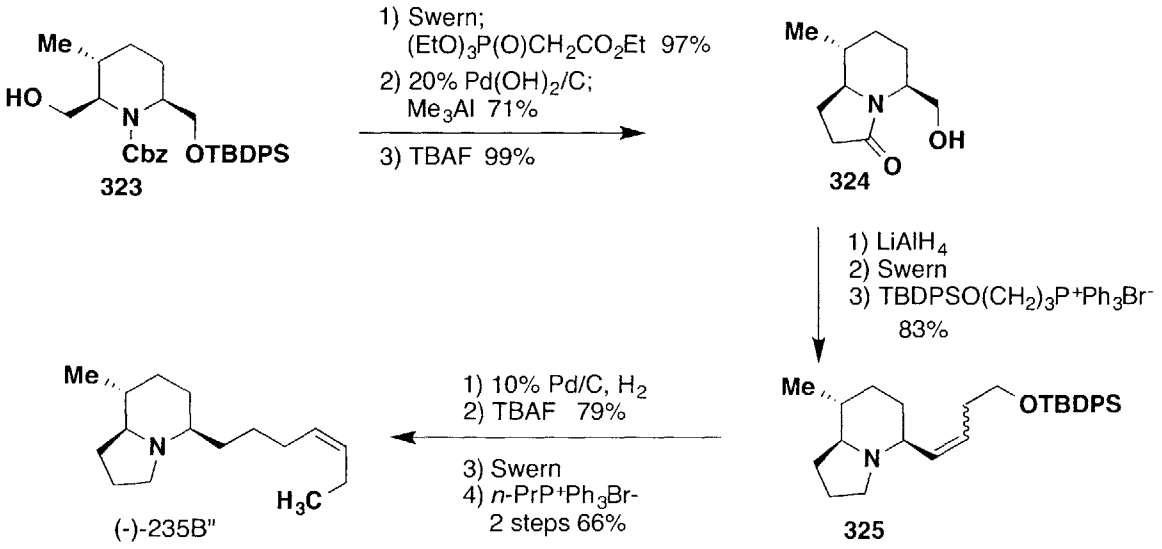
additon to the unsaturated ester installed the methyl substituent on the ring with high stereoselectivity. Carbon extension of one of the substituents began with reduction of the ester to provide alcohol **323**.

Scheme 71



Swern oxidation followed by Horner-Wadsworth-Emmons olefination extended the carbon chain to provide the basis for formation of the 5-membered ring. Reduction of the resulting olefin, hydrogenolysis of the Cbz group, and deprotection of the silyl ether resulted in the cyclized product **324**. Reduction of the lactam followed by stepwise manipulation of the side chain afforded indolizidine 235B" in seven additional steps. Indolizidine (-)-235B' was also synthesized by Toyooka using a similar strategy.

Scheme 72



Although Toyooka demonstrated the elegant use of a chiral piperidine for the synthesis of an indolizidine natural product, the 28-step synthesis is not efficient for the construction of such alkaloids in significant quantities.

Just a year earlier, Toyooka had published the paper describing the absolute stereochemistry of 237D, 235B", and 235B'.[108] That previous paper reported that the absolute stereochemistry of the natural isomer of indolizidine 235B" is 5*S*, 8*S*, 9*R*. In this 2006 publication on the synthesis, Toyooka prepared the levorotatory enantiomer (5*R*, 8*R*, 9*S*) and reported that the positive optical rotation of the natural sample might have been affected by the presence of racemic compound, giving it a positive optical rotation. He does not comment on his 2005 publication, which appeared to conclusively demonstrate that the natural product is dextrorotatory and 5*S*, 8*S*, 9*R*!

In summary, there has been much research in the area of 8-methyl-5-substituted indolizidine synthesis. Several syntheses have been reported to provide 235B' and 235B",

however, they all have disadvantages such as including low yielding reactions or requiring long linear routes.

Chapter 2

Intramolecular Aza Diels-Alder Reactions of Iminoacetonitriles: The Total Syntheses of Indolizidines 235B' and 235B''

As discussed in the previous chapter, there are conflicting reports about which enantiomer of indolizidine 235B" is the natural isomer. All previous syntheses of 235B" furnished either racemic material or the levorotatory isomer (5*R*, 8*R*, 9*S*), however, evidence that the natural isomer of indolizidine 235B" has the 5*S*, 8*S*, 9*R* relative absolute stereochemistry with a positive optical rotation was reported in both the isolation paper[102] and a report by Toyooka[108] in 2005. On the other hand, in 2006 Toyooka reported the synthesis of (-)-235B" and speculated with regard to the original isolation that "the presence of some racemic alkaloid in that sample appears possible." We have developed an efficient route to both (+) and (-)-8-methyl-indolizidines.

Previous members of our laboratory, Kevin Maloney and Jun Chul Choi, completed a synthesis of racemic indolizidine 235B'. It was my goal to optimize the steps in this synthesis and to apply the enantioselective cycloaddition procedure developed by Shaun Fontaine[43] to the key step in the route. In conjunction with this study, I also extended our strategy to the total synthesis of indolizidines (-)-235B" and (+)-235B".

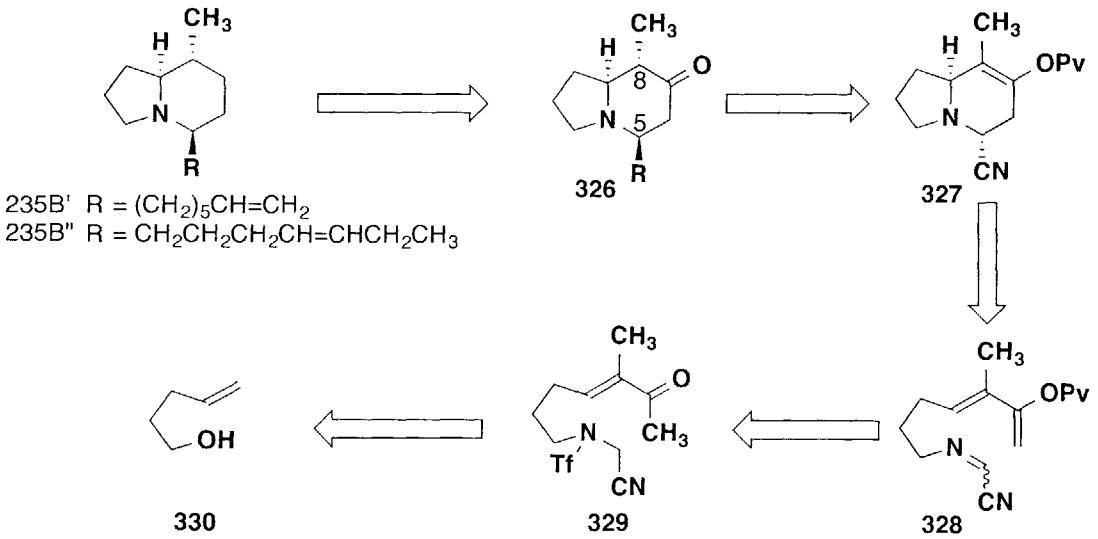
Retrosynthetic Analysis

Both indolizidines 235B' and 235B" are 8-methyl-5-substituted indolizidines, differing with regard to the location of the double bond in their heptenyl C5-substituent. Since the

structures are similar, the retrosynthetic analysis essentially is the same for both targets. Our goal was to develop a synthetic route to both natural products that is more efficient than previous syntheses and has the potential to produce significant quantities of the natural products.

Scheme 73 outlines our retrosynthetic strategy for the synthesis of these indolizidine alkaloids. The key step in our synthesis is the intramolecular [4 + 2] cycloaddition of iminoacetonitrile **328** to produce **327**. The iminoacetonitrile used as the dienophile in the aza Diels-Alder reaction is prepared via a Mitsunobu reaction from commercially available **330**. The diene participating in the cycloaddition is prepared from enone **329** by kinetic deprotonation and trapping of the resulting enolate. All relative stereocenters are set following the key cycloaddition step. Stereoelectronically controlled alkylation/reductive decyanation installs the heptenyl substituent at C5 with the correct relative stereochemistry. Proceeding through a ketone (**326**) derived from the enol ether allows for epimerization of the C8 substituent to the favored equatorial position. Deoxygenation would then provide the indolizidine natural products.

Scheme 73

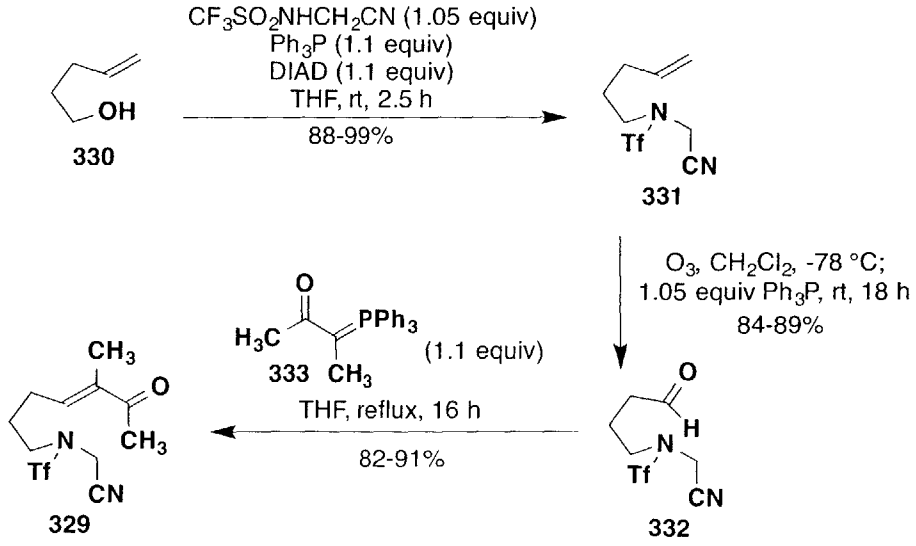


Preparation of the Iminoacetonitrile Cycloaddition Substrate

Enone Preparation

Our route to the key iminoacetonitrile intermediate began with commercially available 4-pentenol (**330**). Mitsunobu reaction of **330** with $TfNHCH_2CN$ (the "Amos reagent") provided the triflamide **331** in excellent yield. Ozonolysis of the terminal double bond followed by Wittig olefination with phosphorane **333**[121] provided enone **329** in high yield as only one isomer. We found that it is not ideal to purify the intermediate aldehyde **332** since some decomposition of the aldehyde occurs on silica gel. Enone **329** can be synthesized in 81% overall yield from **331** by this route without purification of the aldehyde.

Scheme 74



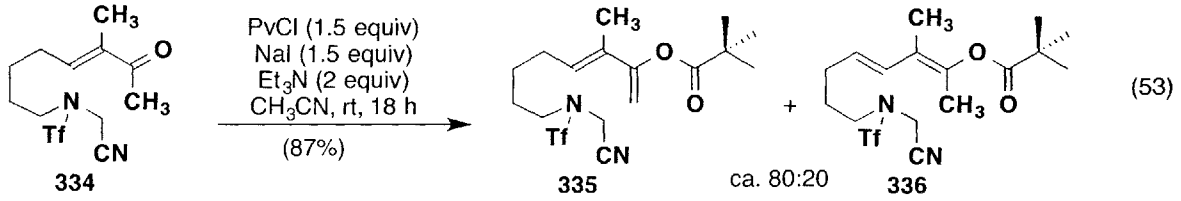
Diene Preparation

In the original study, Maloney synthesized a *tert*-butyldimethylsilyl enol ether as the 4π component for the key Diels-Alder reaction. However, he observed that no cycloaddition of this

[121] Phosphorane **333** was prepared from acetyl chloride and ethyltriphenylphosphonium bromide following the procedure of Aitken, R. A., Atherton, J. I. *J. Chem. Soc., Perkin Trans 1* **1994**, 1281-1284.

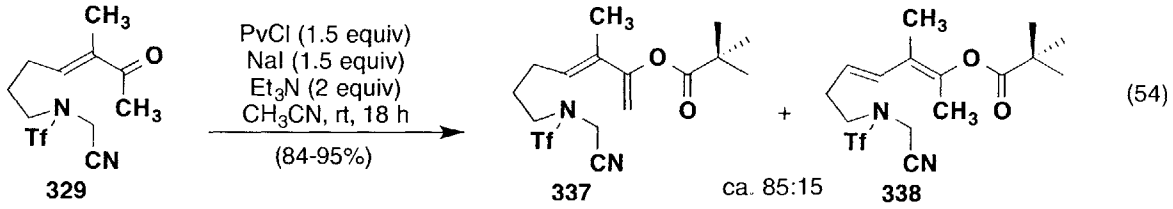
substrate occurred at -78 °C. In the presence of MsOH it was found that warming the reaction mixture to -40 °C and room temperature resulted in decomposition, presumably by reaction of the silyl dienol ether with the acid. The same problem was observed for more stable silyl enol ethers with SiR_3 = Si*t*-BuPh_2 and Si(*i*-Pr)$_3$. Discouraged by these poor results, Maloney next synthesized an enol pivalate to avoid the acid hydrolysis observed with silyl enol ethers, as well as to avoid basic hydrolysis under the trifluoromethanesulfinate elimination conditions.

Later, for a different synthesis, Shaun Fontaine synthesized quinolizidine enol pivalate substrate **335** and observed that diene **335** was formed contaminated with ca. 20% of the undesired isomeric diene **336**. Fontaine tried deprotonation with LDA, *i*-Pr_2EtN, and 2,6-lutidine, but all attempts resulted in a mixture of **335** and **336**.



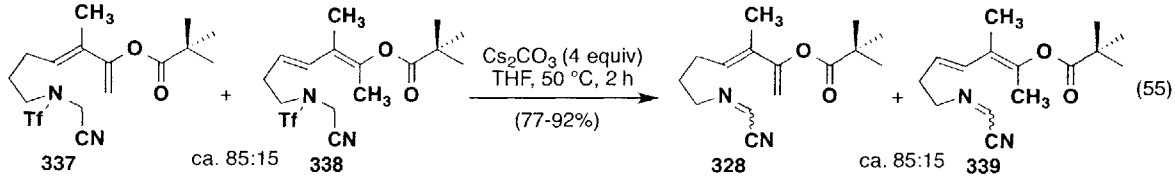
(53)

After careful examination of the ^{1}H NMR spectrum for the indolizidine 235B' we discovered that the enol pivalate **337** prepared by Maloney and Choi was (unbeknownst to them) also contaminated with ca. 15% of isomeric diene **338**. Although the enol pivalate did prove to be more stable than the silyl enol ethers under the cycloaddition conditions, the synthesis of the enol pivalate always produced material contaminated with ca. 15% of the diene isomer **338** (eq 54). Fortunately, we determined that this isomeric diene can be carried through the next two steps in the synthesis without complications and removed from the cycloadduct during column chromatography.



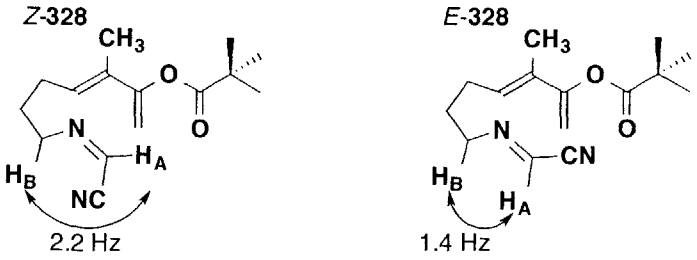
Preparation of the Iminoacetonitrile

With the enol pivalate in hand, elimination of trifluoromethanesulfinate by gently warming the mixture of **337** and **338** in THF in the presence of Cs_2CO_3[122] furnished **328** in excellent yield as a 75:25 mixture of *E* and *Z* imines (eq 55). The undesired isomeric diene is carried through this elimination step and is converted to **339**. Extended reaction times or stirring at 55 °C resulted in lower yields due to decomposition of the iminoacetonitriles.



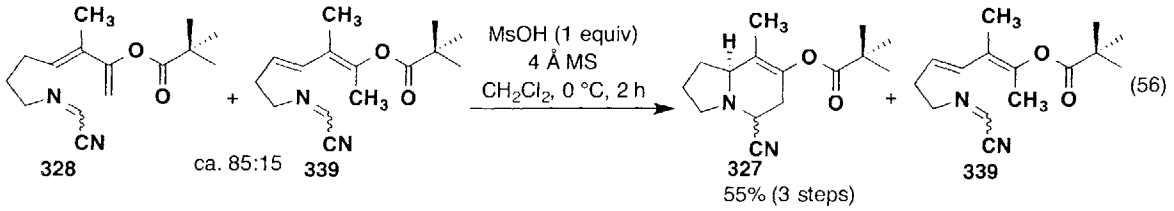
The stereochemistry of the iminoacetonitriles was determined using the same approach discussed on page 34. The ^{1}H NMR spectra revealed a four-bond coupling (^{4}J) between the iminyl proton (H_A) and H_B. This ^{4}J coupling constant provides good evidence for the imine geometry. The *Z*-imine has a transoidal relationship between H_A and H_B, which produces a larger coupling constant.

[122] A significant decrease in reactivity of the Cs_2CO_3 was observed after a few months stored under argon in a desiccator. Recently purchased reagent provided the best yields in the elimination reaction.



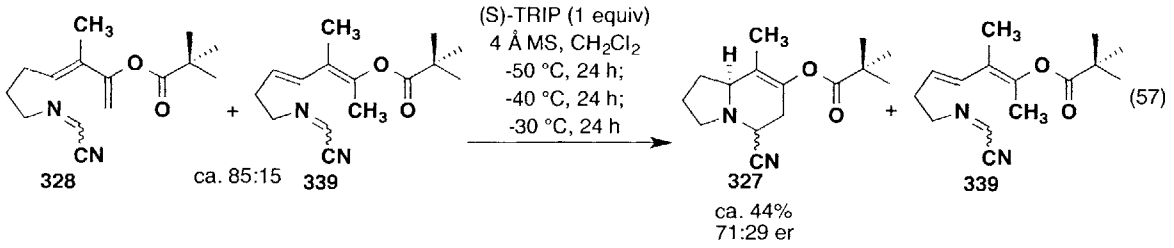
Intramolecular [4 + 2] Cycloaddition

The aza Diels-Alder reaction of iminoacetonitrile **328** (contaminated with **339**) proceeds at 0 °C in the presence of 1 equivalent of methanesulfonic acid (MsOH). 4 Å Molecular sieves were added as a precautionary measure to remove any adventitious water. Due to the ability of the enol pivalate to tolerate acidic conditions, the reaction can be run at higher temperatures than -78 °C without decomposition. Cycloadduct **327** was produced in 55% overall yield from enone **329** as a mixture of inconsequential cyano epimers. The iminoacetonitrile contaminant **339** with the isomeric diene does not react under the conditions of the cycloaddition and can be separated from **327** via column chromatography.

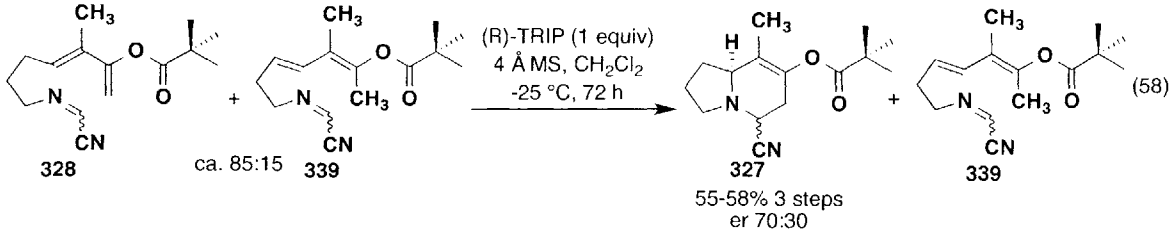


Methanesulfonic acid is an excellent promoter of the intramolecular [4 + 2] cycloaddition of iminoacetonitrile **328**; however, the goal of my research was to use a chiral Brønsted acid to promote an enantioselective cycloaddition. Shaun Fontaine had optimized the conditions for the enantioselective cycloadditions of iminoacetonitriles. He observed in a quinolizidine prototype case that higher temperatures (0 °C and rt) erode the er of the cycloadduct significantly (from 93:7 to 81:19 er). Maintaining a low reaction temperature (-55 °C) improved the er (93:7), but ca. 20-25% of the iminoacetonitrile remained after 21 h. Fontaine tested the enantioselective

cycloaddition conditions for the indolizidine 235B' substrate and obtained a low yield and ca. 71:29 er (eq 57).[123] The low er for indolizidine cycloadducts was also observed for another substrate studied by Fontaine.



After extensive screening studies, Fontaine determined that reaction at -25 °C allows for a reasonable rate of cycloaddition without a decrease in enantioselectivity. We found that the [4 + 2] cycloaddition of **328** in the presence of 1 equiv of (*R*)-TRIP proceeds at -25 °C over 72 h to afford cycloadduct **327** in 55-58% overall yield from enone **329** as a 90:10 mixture of cyano epimers with each produced in an 70:30 er (eq 58). We are able to heat the mixture of epimeric cycloadducts in acetonitrile to equilibrate them for structure assignments and to aid in purification, but in preparative work there is no need for this step since this stereocenter is destroyed during subsequent synthetic elaboration. It was observed by Maloney that cycloadditions to afford indolizidines are generally slower than those leading to quinolizidines. Performing the aza Diels-Alder reaction at -25 °C is warm enough for the cycloaddition to occur without erosion of the enantiomeric excess.



[123] The yield was erroneously calculated as if **328** was pure iminoacetonitrile and not contaminated with **339**.

The enantioselective cycloaddition of **328** does require 1 equivalent of (*R*)-TRIP.[124] Fortunately, TRIP can be recovered by extraction after the cycloadditions in 89-95% yield, and used in subsequent cycloadditions directly with no difference in results.

The determination of enantiomeric excess was conducted by making the (*R*)-BNPA ((*R*)-(−)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate) salt of the cycloadducts and determining the diastereomeric ratio by ^{1}H NMR spectroscopy. The ratio was also confirmed by the same technique after the next step of the synthesis.

Alkylation/Reductive Decyanation of the α-Amino Nitrile Cycloadduct

After completing the key cycloaddition step in the synthesis, we then turned our attention to installing the C5-substituent found in the natural products. The strategy we employed was based on an alkylation/reductive decyanation sequence that we expected would provide access to the correct stereochemistry at C5.

Alkylation of the 235B′ Substrate

Indolizidine 235B′ has a 6-heptenyl substituent at C5, so commercially available 7-bromoheptene was used as the alkylating agent. Alkylation proceeded smoothly using excess LDA,[125] however Maloney observed that the reductive decyanation with several hydride reagents ($NaBH_4$, $ZnBH_4$, $NaBH_3CN$) afforded a complex mixture of products. Maloney then decided to pursue a radical-mediated reductive decyanation strategy using Na/NH_3 to avoid the formation of iminium ions that were thought to be the cause of decomposition. An exciting observation was that under dissolving metal conditions the enol pivalate was also cleaved. The enol pivalate

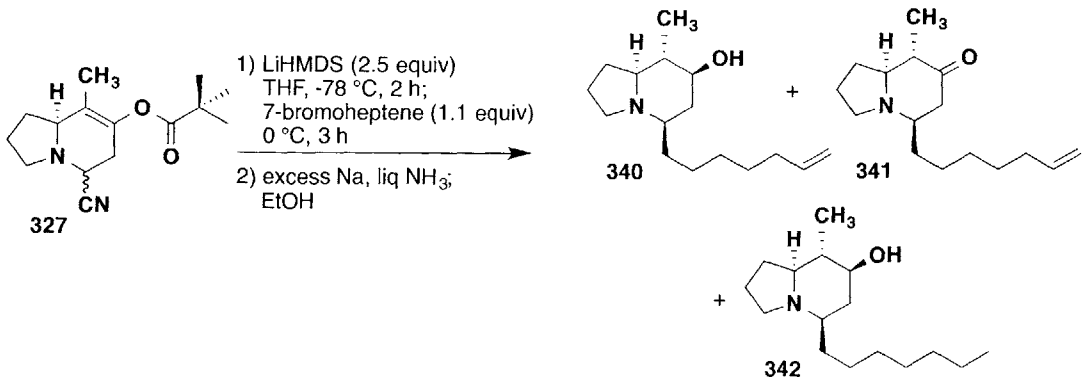
[124] Using 0.3 equiv of (R)-TRIP resulted in an incomplete reaction at -25 °C and the cycloadduct was isolated in 28 % yield (ca. 85% pure).
[125] We currently use LiHMDS which results in a cleaner alkylation.

needs to be converted to the ketone during the synthesis, so this simultaneous cleavage in the same pot as reductive decyanation would save a step in the synthesis. Maloney isolated the cyclic ketone from the dissolving metal reaction, but deoxygenation via a tosylhydrazone proved to be difficult. Maloney later observed that the addition of ethanol to the sodium/liquid ammonia reduction provided alcohol **340** as a single diastereomer. Jun Chul Choi worked to optimize the reduction conditions for this reaction using excess sodium.

There are several transformations taking place under the dissolving metal conditions of this step in our synthesis. Reductive decyanation occurs quickly under the reaction conditions. The enol pivalate is also cleaved to generate an enolate. Protonation by ethanol affords the respective ketone, which is reduced under the dissolving metal conditions to afford a secondary alcohol. During the course of the reaction the C8 methyl substituent also epimerizes to the thermodynamically favored equatorial position.

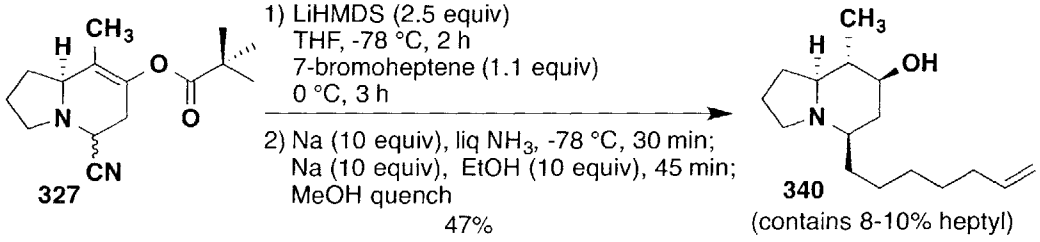
We observed that the conditions developed by Choi did not afford solely the desired product. Using 25 equivalents of freshly cut sodium and 10 equivalents of ethanol and quenching the reaction mixture with either additional ethanol or saturated aqueous NH_4Cl solution resulted in ketone **341** as the major product. Adding sodium in two portions of 25 equivalents each resulted in none of ketone **341** but significant (ca. 20%) amounts of **342**, the product of reduction of the alkene bond.[126]

[126] For examples of olefin reduction under dissolving metal conditions, see: Pearson, A. J.; Perrior, T. R. *J. Organomet. Chem.* **1985**, 285-253.



(59)

Reducing the amount of sodium to two 10 equivalent portions improved the result and only ca. 10% of **342** was observed with the major product being the desired indolizidinol **340** (eq 60). The small amount of indolizidine containing the fully saturated side chain can be removed in the next step of the synthesis by column chromatography.

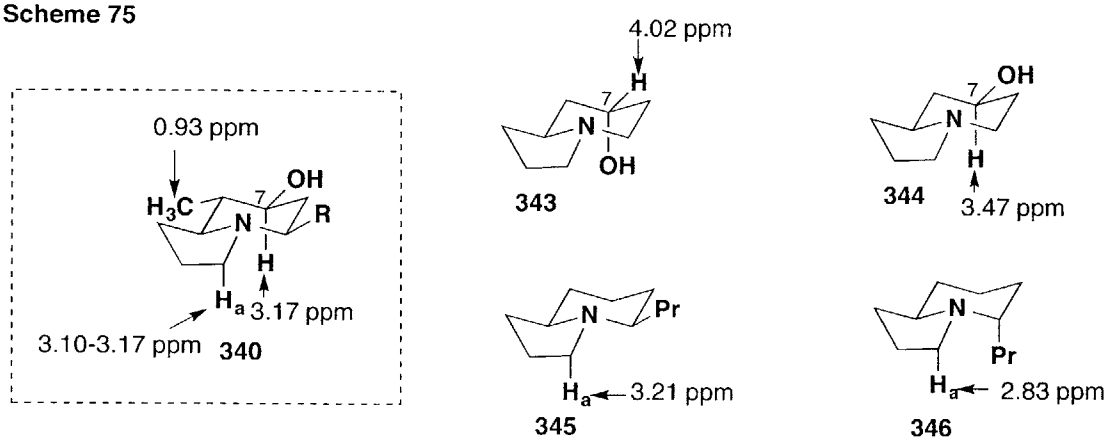


(60)

The stereochemistry of both the hydroxyl group and C5-substituent was assigned by ^{1}H NMR comparison with spectral data reported in the literature (Scheme 75). The stereochemistry at C5 was assigned based on previous transformations of indolizidines performed in our group as well as a comparison to compounds **345** and **346** reported by Polniaszek. [46a,d] Polnaiszek synthesized both indolizidines **345** and **346** using either propylmagnesium bromide or alkylation/reductive decyanation reactions with the respective α-amino nitrile. Thorough 1D and 2D NMR experiments, including NOE, he was able to assign the structures of each indolizidine. We compared the data for our indolizidinol **340** to that reported by Polnaiszek and observed a similar deshielded proton H_a, indicating that the C5 heptenyl group has an equatorial

configuration. To determine the stereochemistry of the hydroxyl group, we compared ^{1}H NMR data for indolizidinol **340** to the alcohols **343** and **344** reported by Rader.[127] Rader assigned the stereochemistry of 7- and 8-hydroxyindolizidines by IR, NMR, and pK_a analysis. Strong Bohlmann bands suggested **343** and **344** contained *trans*-fused rings. Rader also identified an upfield shift for the axial proton at C7 in **344**. An equatorial proton is often shifted downfield as observed for indolizidine **343**. The upfield axial proton resonance for **340** supports our assignment.

Scheme 75

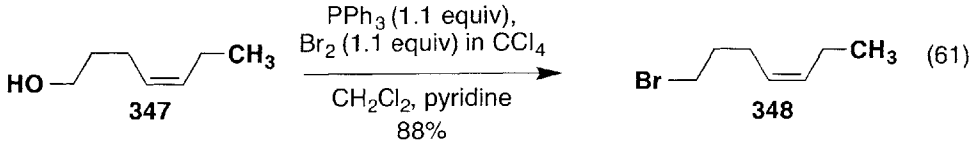


Alkylation of 235B'' Substrate

Indolizidine 235B'' has a heptenyl substituent at C5 with an internal olefin. We hoped that the internal olefin would be more stable under dissolving metal conditions and not be reduced like the terminal olefin in the 235B' substrate. The electrophile required for alkylation in this case is not commercially available but can be made in one step from the corresponding alcohol (eq 61).[128]

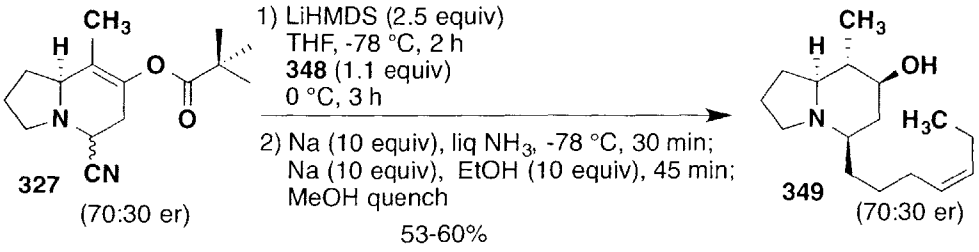
[127] Rader, C. P.; Young, R. L.; Aaron, H. S. *J. Org. Chem.* **1965**, *30*, 1536

[128] Alkenyl bromide **348** was prepared via a literature procedure: Joshi, N. N.; Mamdapur, V. R.; Chadha, M. S. *J. Chem. Soc. Perkin Trans. 1* **1983**, 2963-2966



Alkylation of cycloadduct **327** with bromide **348** proceeded smoothly. Deprotonation with LiHMDS results in a cleaner alkylation than when LDA is used. The alkylated product is isolated following workup and immediately exposed to the dissolving metal conditions. The substrate is initially added to a solution of 10 equivalents of sodium in liquid ammonia. After 30 min, an additional 10 equivalents of sodium is added in order to make sure that active sodium is still present in the reaction mixture. The second addition of freshly cut sodium is necessary or unreacted ketone is observed following workup. The use of a single portion of 25 equivalents of sodium at the beginning of the reaction also leads to isolation of the cyclic ketone as the major product. It is possible that during the course of the reaction the sodium in the reaction flask becomes coated and rendered unreactive. Addition of ethanol then leads to protonation of the enolate to generate the ketone, but there is no active sodium present to reduce the carbonyl group. We solved this by adding a second portion of sodium before the flask is charged with ethanol. Methanol is used to quench the excess sodium at -78 °C, and the reaction mixture is allowed to slowly warm to room temperature. No ketone is observed under these conditions and indolizidinol **349** (70:30 er) is isolated in 53-60% yield over two steps.

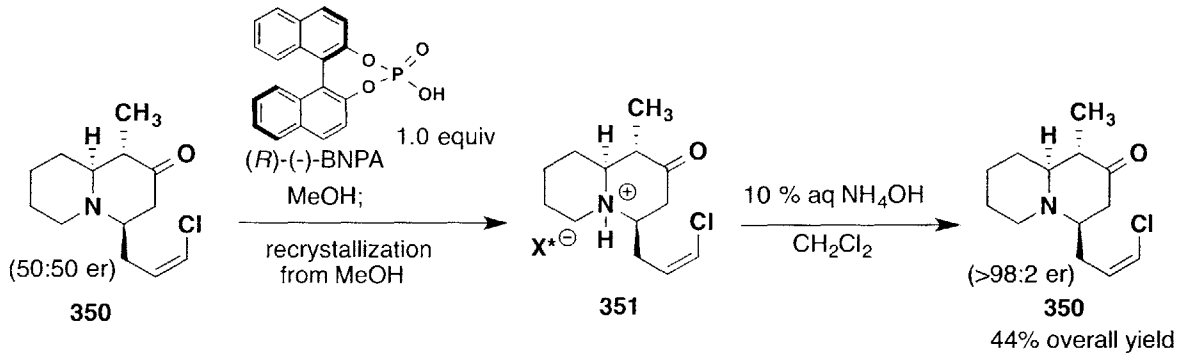
Scheme 76



Enantiomeric Enrichment

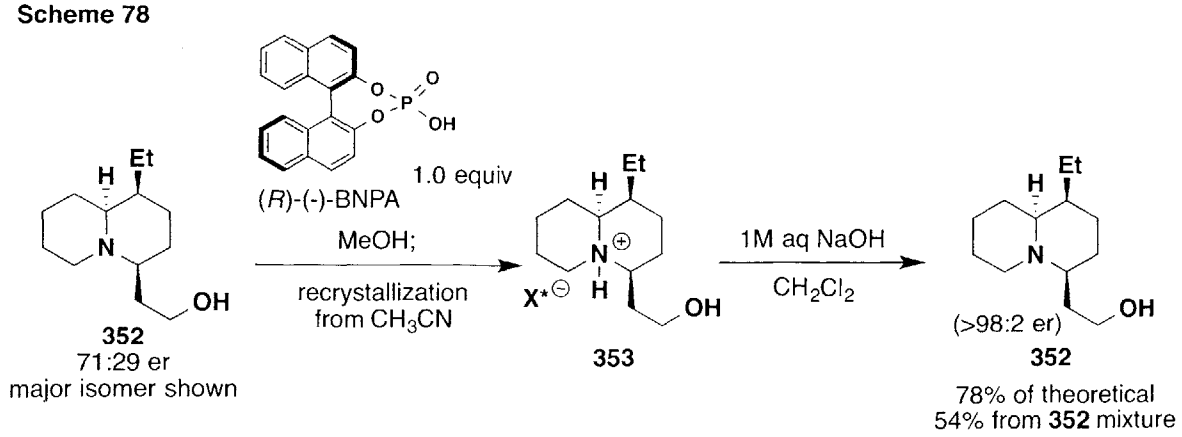
In order to increase the enantiomeric purity of our intermediates, the two indolizidine enantiomers were separated by recrystallization of diastereomeric indolizidinol salts. Based on the previous success with resolutions of quinolizidines in our group, (*R*)-(−)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate ((*R*)-BNPA) was chosen as the resolving agent. Kevin Maloney had performed a resolution of racemic quinolizidine **350a** with this acid in the course of the synthesis of 217A (Scheme 77).[41]

Scheme 77



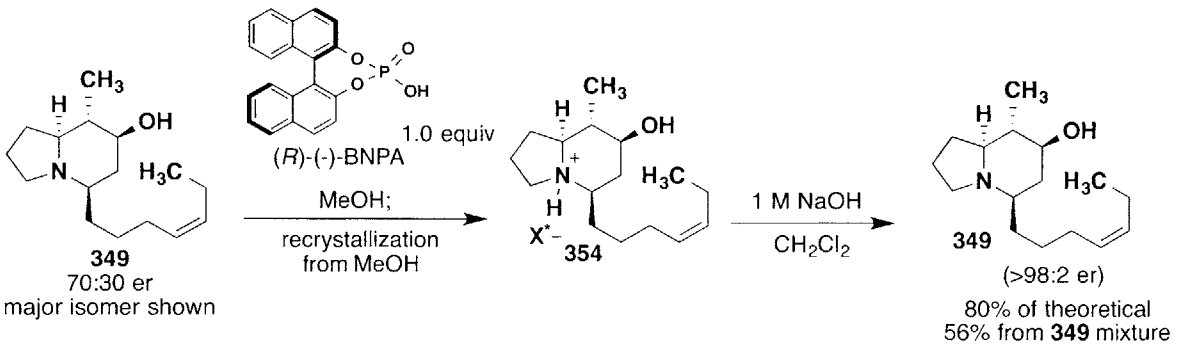
Subsequently, Shaun Fontaine employed the same acid for the enantiomeric enrichment of an intermediate in his synthesis of quinolizidine (-)-207I (Scheme 78).[43] Recrystallization of intermediate **352** (71:29 er) in warm acetonitrile afforded **352** (>98:2 er) in 54% yield from the **352** mixture of enantiomers.

Scheme 78



Indolizidinol **349** (70:30 er) and (*R*)-(−)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate ((*R*)-BNPA) were dissolved in methanol and then concentrated to afford a white solid. Initially, we were synthesizing the levorotatory enantiomer and decided to use (*R*)-BNPA based on the results shown above. It turned out that using (*R*)-BNPA did result in the correct enantiomer. ^{1}H NMR analysis of this material indicated a 70:30 dr for this mixture (Figure 20a). Recrystallization from hot methanol afforded the (-)-indolizidinol-(*R*)-BNPA salt (>98:2 dr, Figure 20b). A second crop afforded more of the salt with the same dr; however, further recrystallization of the mother liquor usually resulted in material with poor dr. The salt was stirred in 1 M NaOH and CH_2Cl_2 to form the free amine that was obtained in 56% overall yield from the mixture of enantiomers **349** (Scheme 79). The mixture of indolizidinol salts in the mother liquor can also be deprotonated and then converted to a (*S*)-BNPA salt following the same procedure. Recrystallization furnishes the (+)-indolizidinol **349** (>98:2 er).

Scheme 79



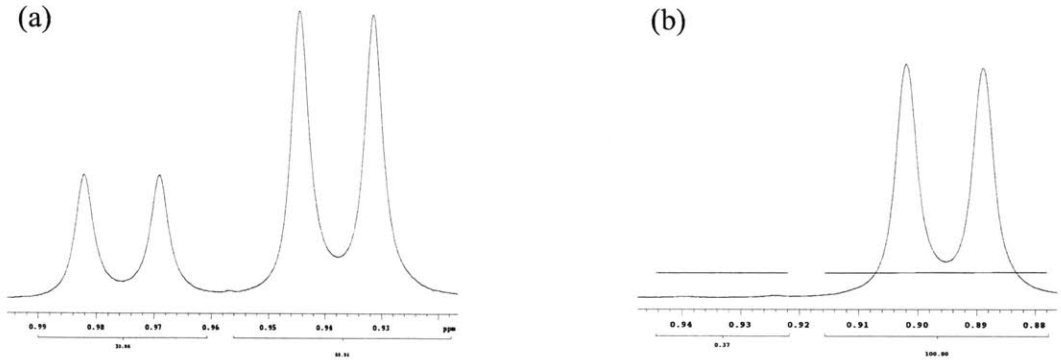


Figure 20. (a) ^{1}H NMR spectrum of **349** indicates a 70:30 dr of (R)-BNPA salts. (b) ^{1}H NMR of **349** after recrystallization indicates a >98:2 dr of (R)-BNPA salts after recrystallization.

The enantiomeric enrichment of the **340** by forming the (*R*)-BNPA salt following the same procedure and recrystallizing from methanol afforded indolizidinol with er >98:2 er in 51% yield from the mixture of enantiomers of **340**.

Deoxygenation Strategy

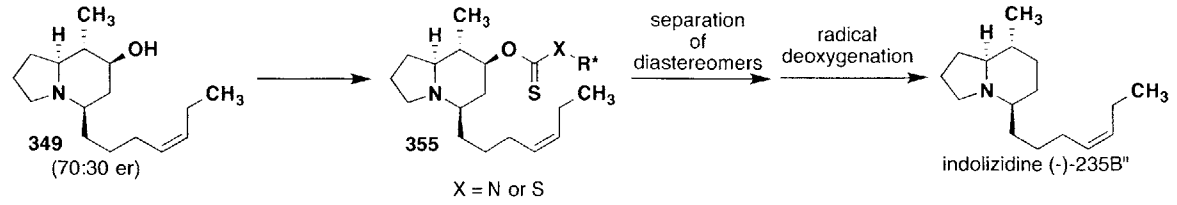
One of the most common methods for deoxygenation of alcohols is the Barton-McCombie deoxygenation.[129,130] Our original strategy for deoxygenation of **349** was to use this step as a means of simultaneously performing a resolution. The goal was to make a chiral xanthate or similar derivative for radical deoxygenation (Scheme 80). Installing a chiral functional group would potentially allow separation of the diastereomers via recrystallization or chiral HPLC, and this would eliminate the need for additional steps in the synthesis.

---

[129] (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574-1585. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901-3924. (c) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *47*, 8969-8984. (d) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. C. *Tetrahedron* **1992**, *48*, 7435-7446.

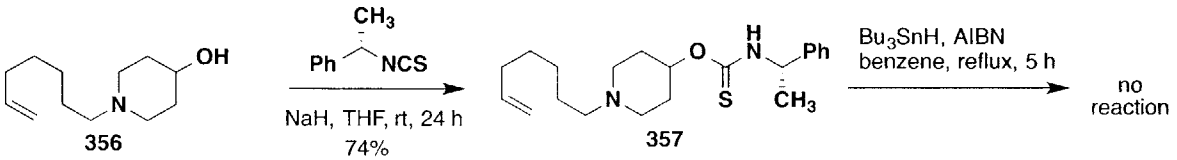
[130] For reviews on radical-mediated deoxygenation, see: (a) Hartwig, W. *Tetrahedron* **1983**, 39, 2609-2645. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413-1432. (c) McCombie, S. W. Reduction of Saturated Alcohols and Amines to Alkanes. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Elsevier Ltd: Oxford, UK, 1991; Vol. 8, pp 811-833. (d) Zard, S. *Radical Reactions in Organic Synthesis*, Oxford University Press Inc: New York, 2003. (e) Zard, S. Z. Xanthates and Related Derivatives as Radical Precursors. In *Radicals in Organic Synthesis*, Renaud, P.; Sibi, M. P. Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 90-108. (f) McCombie, S. W.; Motherwell, W. B.; Tozer, M. J. *Org. React.* **2012**, *77*, 161-592.

Scheme 80



The feasibility of this strategy was investigated using **356** as a model alcohol. One of the first chiral model substrates made was **357**. Reaction of the model alcohol **356** with phenethylisothiocyanate[131] afforded thiocarbamate **357** in good yield. Unfortunately the resulting thiocarbamate does not fragment under typical radical deoxygenation conditions. Thiocarbamates have been used in radical deoxygenation; however, an aryl group is always the substituent on the thiocarbamate.[132]

Scheme 81

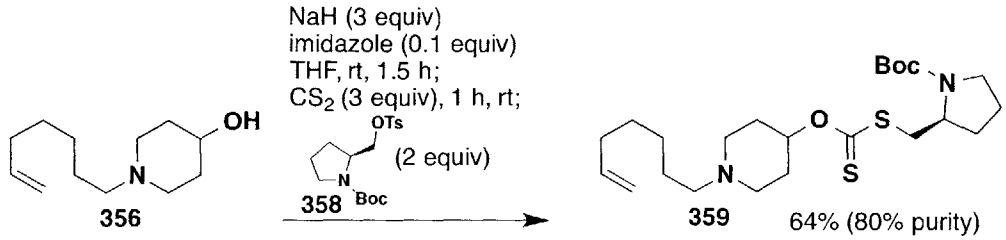


Another strategy we investigated involved the reaction of alcohol **356** with carbon disulfide and then a chiral electrophile to generate a chiral xanthate derivative. Boc-Proline derivative **358** was synthesized in two steps from (*S*)-prolinol. Reaction of the model alcohol with CS_2 and then **358** afforded the desired xanthate **359** with only 80% purity due to unidentified byproducts formed during the reaction that could not be separated by column

[131] For preparation of this isothiocyanate, see: (a) Yella, R.; Ghosh, H.; Murru, S.; Sahoo, S. K.; Patel, B. K. *Synth. Commun.* **2010**, *40*, 2083-2096. (b) Munch, H.; Hansen, J. S.; Pittelkow, M.; Christensen, J. B.; Boas, U. *Tetrahedron Lett.* **2008**, *49*, 3117-3119.

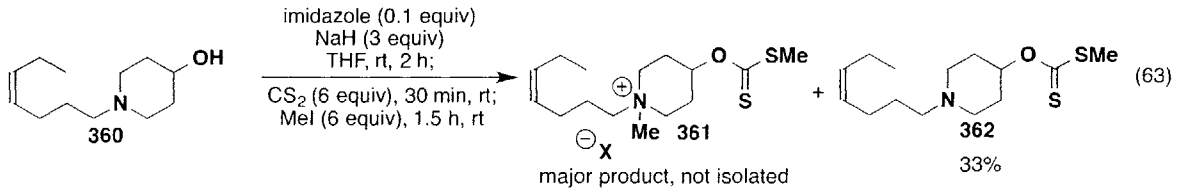
[132] For radical deoxygenation using thiocarbamates, see: (a) Oba, M.; Nishiyama, K. *Tetrahedron* **1994**, *50*, 10193-10200. (b) Oba, M.; Suyma, M.; Shimamura, A.; Nishiyama, K. *Tetrahedron Lett.* **2003**, *44*, 4027-4029. (c) Yamashita, S.; Kitajima, K.; Iso, K..; Hirama, M. *Tetrahedron Lett.* **2009**, *50*, 3277-3279. (d) Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408-2425.

chromatography. Due to the difficulty isolating pure **359** and the difficulties encountered synthesizing other chiral xanthate derivatives, we decided to abandon this approach.



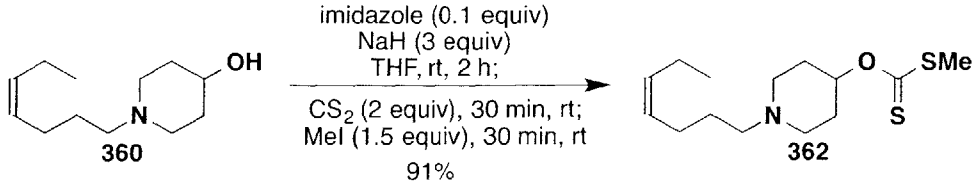
(62)

We then turned our attention to conventional deoxygenation methods proceeding via S-methyl dithiocarbonate derivatives. Jun Chul Choi had initially explored conditions for the synthesis of S-methyl dithiocarbonate derivatives;[133] however, we observed significant alkylation of the tertiary amine with MeI under the conditions that had been reported to be effective by Choi. Optimization studies were therefore carried out using the model alcohol **360**. Under standard Barton-McCombie conditions, the desired S-methyl dithiocarbonate **362** was obtained along with the undesired alkylation product **361** as shown in eq 63.



(63)

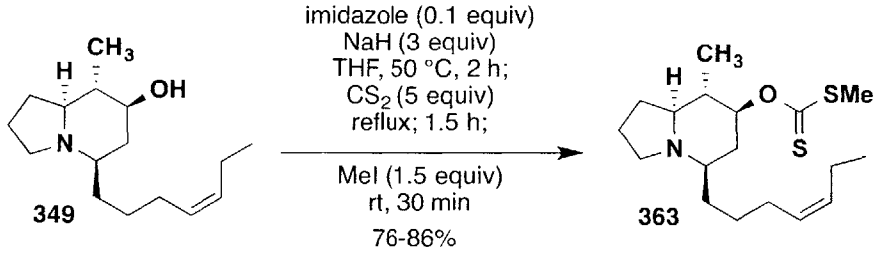
After further studies, it was found that reducing the amount of carbon disulfide to 2 equivalents and methyl iodide to 1.5 equivalents led to the formation of **362** in 91% yield (eq 64).



(64)

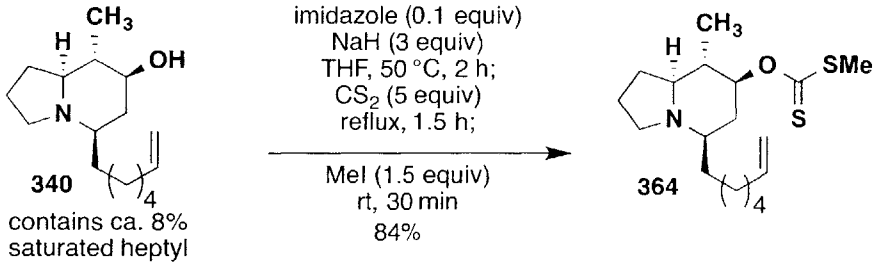
[133] For the synthesis of a methyldithiocarbonate involving a similar indolizidine system, see: Brandi, A.; Cordero, F.; Querci, C. *J. Org. Chem.* **1989**, *54*, 1748-1750.

Applying the exact conditions from this model study to the indolizidine substrate **349** resulted in a low yield due to incomplete reaction of this more sterically hindered alcohol with CS_2. The optimized conditions for this transformation proved to involve heating the alcohol in the presence of 3 equivalents of NaH for two hours, adding 5 equivalents of CS_2 and heating the mixture for 1.5 h, and then cooling to room temperature. MeI (1.5 equiv) is added and the reaction mixture is then stirred for an additional 30 min at room temperature. Addition of 1.5 equiv of MeI is sufficient to afford **363** in 76-86% yield (eq 65).



(65)

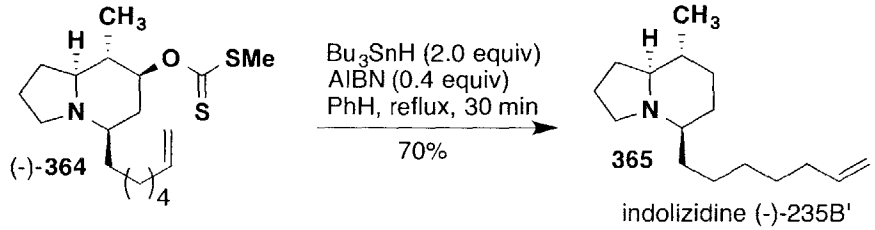
These conditions were also applied to the alcohol intermediate **340** involved in the total synthesis of indolizidine 235B' (eq 66). Indolizidinol **340** (contaminated with ca. 8% of compound with saturated side chain) reacts with CS_2 and MeI to afford **364** in 84% yield. The contaminant with a fully saturated side chain was removed during column chromatography.



(66)

Radical Deoxygenation of the 235B' Precursor

With the two dithiocarbonates in hand, the final step in each total synthesis was the radical deoxygenation step. Deoxygenation of (-)-**364** using *n*-Bu_3SnH and catalytic AIBN in refluxing benzene under standard Barton-McCombie conditions provided indolizidine (-)-235B' ($[\alpha]^{24}_D$ -69.1 (*c* 1.0, MeOH)) in 70% yield.



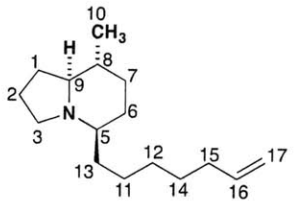
(67)

The ^1H NMR data for our synthetic indolizidine (-)-235B' was compared to the data reported in the literature by Toyooka, Holmes, and Daly (Table 7). There is good agreement in the proton spectra, especially the well-defined protons of the methyl group and alkene.

The ^{13}C NMR data is shown in Table 8. Toyooka references $CDCl_3$ to 77.00 ppm resulting in a small difference for all carbon resonances relative to our ^{13}C NMR data. There was no ^{13}C NMR data for indolizidine 235B' reported in the isolation paper.

The optical rotation of our synthetic indolizidine (-)-235B' was in good agreement with that reported by Daly for the sample isolated from nature. Toyooka reports the optical rotation to be $[\alpha]^{26}_D$ -98.8 (*c* 0.89, MeOH), which is different from what we observe. Toyooka suggests that the optical rotation for the sample isolated by Daly is low because of "insufficient fractionation" due to the low concentration used to determine optical rotation. It is unclear how Toyooka determined the enantiomeric purity of his samples. We determined enantiomeric purity by forming the (R)-BNPA salt of the indolizidines and analyzing the sample by ^1H NMR on a 500 MHz instrument.

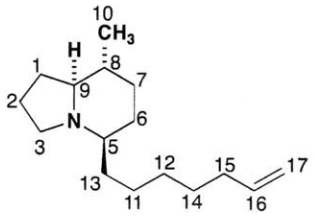
Table 7. Comparison of ^{1}H NMR and optical rotation data for indolizidine (-)-235B'



Indolizidine (-)-235B'

This Work (500 MHz, $CDCl_3$, 7.27 ppm)			Toyooka[119] (500 MHz, $CDCl_3$, 7.26 ppm)		Holmes[112] (400 MHz, $CDCl_3$)		Daly[101] (300 MHz, $CDCl_3$)	
Atom	**δ**	***J***	**δ**	***J***	**δ**	***J***	**δ**	***J***
10	0.87	d, J = 6.6 Hz	0.85	d, J = 6.5 Hz	0.83	d, J = 6.5 Hz	0.89	d, J = 6.2 Hz
6	0.95	m	0.94	m	-	-	-	-
7,8,9, 11,12, 13,14	1.17-1.51	m, 12 H	-	-	-	-	-	-
1	1.64	m	-	-	-	-	-	-
2,6	1.70-1.77	m	-	-	-	-	-	-
5	1.84	m	-	-	-	-	-	-
1	1.88-1.94	m	-	-	-	-	-	-
3	1.96	app q, J = 9.0 Hz						
15	2.05	app q, J = 7.0 Hz	2.03	q-like, J = 7.0 Hz	2.00	dt, J = 7.0, 7.0 Hz	2.49	br
3	3.26	td, J = 8.8, 1.9 Hz	3.25	td, J = 9.0, 2.0 Hz	3.23	ddd, J =8.7, 8.7, 2.0 Hz	3.27	br t
17	4.93	ddt, J = 10.1, 2.1, 1.2 Hz	4.92	dm, J = 10.0 Hz	4.89	ddt, J = 10.2, 1.0, 1.1 Hz	4.95	m
17	4.99	ddt, J = 17.1, 2.1, 1.6 Hz	4.98	dm, J = 17.0 Hz	4.95	dd, J = 16.9, 1.6 Hz	4.95	m
16	5.81	ddt, J = 17.2, 10.3, 6.7 Hz	5.80	ddt, J = 17.0, 10.0, 6.9 Hz	5.77	ddt, J = 16.9, 10.2, 6.7 Hz	5.31	m
			1.16-1.50	br m, 10 H	0.86-1.95	m, 20 H	1.0-2.15	br m, 22 H
			1.58-1.77	br m, 5 H	-	-	1.86	br, 1 H
			1.80-1.97	br m, 4 H	-	-	1.45	br, 1 H
			-	-	-	-	1.05	br, 1 H
optical rotation	$[\alpha]^{24}_D$ -69.1 (*c* 1.0, MeOH)		$[\alpha]^{26}_D$ -98.8 (*c* 0.89, MeOH)		--		$[\alpha]^{25}_D$ -61 (*c* 0.5, MeOH)	

Table 8. Comparison of ^{13}C NMR data for indolizidine 235B'



Indolizidine (-)-235B'

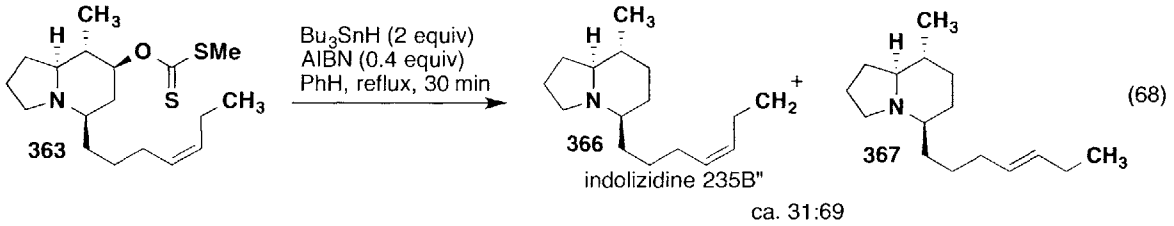
	(-)-235B' This Work[a] ($CDCl_3$ 125 MHz)	(-)-235B' Toyooka[b,119] $CDCl_3$	(+/-)-235B' Holmes[112] ($CDCl_3$, 100 MHz)
Carbon	**δ**	**δ**	**δ**
1	29.3	29.04	29.0
2	31.5	31.22	31.2
3	52.1	51.83	51.8
5	63.7	63.49	63.5
6	34.0	33.68	33.65
8	36.8	36.56	36.5
9	71.5	71.31	71.3
10	19.1	18.88	18.9
7, 11, 12, 13, 14	34.8, 29.8, 29.1, 25.9, 20.6	34.56, 29.53, 28.87, 25.66, 20.33	34.5, 29.5, 28.8, 25.6, 20.3
15	33.9	33.74	33.71
16	139.3	139.14	139.1
17	114.4	114.16	114.1

[a] $CDCl_3$ was referenced to 77.23 ppm

[b] $CDCl_3$ was referenced to 77.00 ppm

Deoxygenation of the 235B" Precursor

Radical deoxygenation of the intermediate for the synthesis of 235B" was not trivial. Using the same conditions as those employed for the 235B' substrate (eq 67), the major product was **367** in which E/Z alkene isomerization had occurred (eq 68). We then began examining modification of the reaction conditions with the goal of suppressing the isomerization. Reducing the amount of *n*-Bu_3SnH from 2 to 1.5 equivalents in toluene at reflux for 3 h resulted in a mixture of olefin isomers[134] and unreacted xanthate (ca. 25%). However, for reasons that remain unclear another run with 1.5 equiv Bu_3SnH in refluxing toluene over 3 h resulted in less olefin isomerization.



The inconsistent results using Bu_3SnH as the hydrogen donor led us to examine other organotin reagents. In 1992, Johnson and Poulos reported that when performing a radical deoxygenation with (trimethylsilyl)silane they observed isomerization of a cis to trans alkene.[135] Although a different hydride reagent was involved in this study, they also report that *n*-Bu_3SnH showed minimal (<10%) isomerization. This paper does suggest that isomerization of *Z*-olefins can occur under the radical deoxygenation conditions and the extent of isomerization can vary with the choice of hydride reagent.

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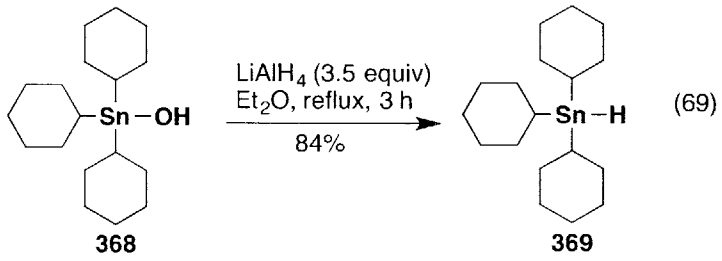
[134] The ratio of olefin isomers was not determined due to overlap of the alkene protons from the xanthate in the crude ^1H NMR spectrum.

[135] Johnson, D. W.; Poulos, A. *Tetrahedron Lett.* **1992**, *33*, 2045-2048.

In 1988, Corey and Mehrotra observed tributyltin addition to an alkyne[136] under radical conditions and found that the more bulky reagent tricyclohexyltin hydride exhibits less tendency toward addition. Earlier Rahm and Grimeau had examined the reactivity of tricyclohexyltin hydride with norbornene and observed no reaction under free radical or under high-pressure conditions.[137]

The examples in the literature of the reduced tendency of tricyclohexyltin hydride to add to π-bonds led us to believe that this tin reagent might give improved results in our radical deoxygenation. Tricyclohexyltin hydride (**369**) was prepared from tricyclohexylhydroxytin (**368**) in one step using excess $LiAlH_4$ following a literature procedure (eq 69).[138]



368 **369** (69)

We performed a control experiment with Cy_3SnH and n-Bu_3SnH to investigate their ability to cause isomerization of the olefin in the deoxygenated product **370b** (Table 9). As we predicted, the bulkier reagent Cy_3SnH is slower to cause isomerization of the olefin. We imagine isomerization is occurring by tin radical addition to the olefin in a reversible process. These control experiments indicated that Cy_3SnH is in fact the better choice for our deoxygenation reaction.

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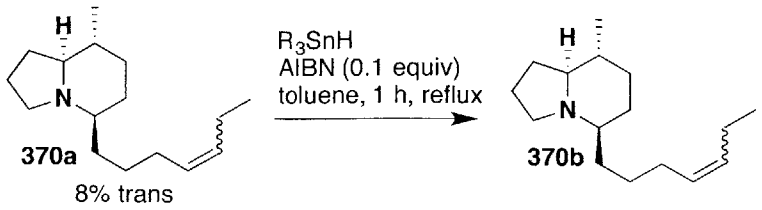
[136] Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, *29*, 57-60.
[137] Rahm, A. Grimeau, J. *J. Organomet. Chem.* **1985**, *286*, 297-304.
[138] Jousseaume, B.; Lahcini, M.; Rascle, M.-C. *Organometallics*, **1995**, *14*, 685-689.

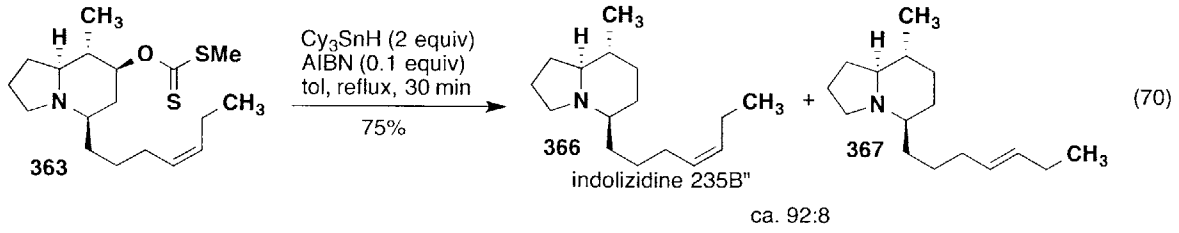
Table 9. Isomerization experiment with *n*-Bu_3SnH and Cy_3SnH.



entry	conditions	**370b** cis/trans ratio[a]
1	Cy_3SnH (1.0 equiv)	75:25
2	*n*-Bu_3SnH (1.0 equiv)	58:42

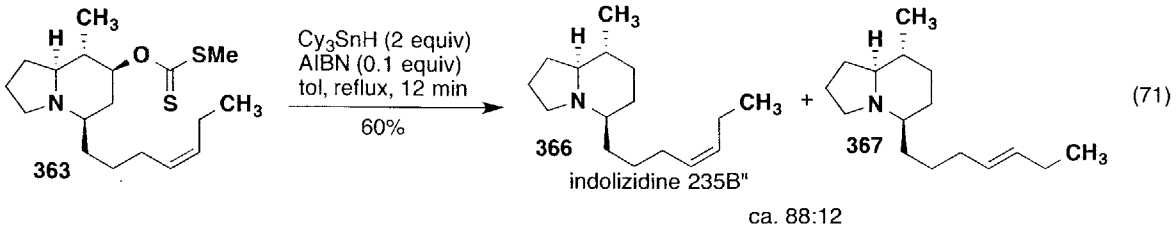
[a] Ratio of products was determined by ^1H NMR

Radical deoxygenation of **363** with Cy_3SnH and catalytic AIBN in refluxing toluene afforded primarily indolizidine 235B" (**266**) contaminated with only ca. 8% of the isomerization product **367**. It is difficult to monitor this reaction by TLC since a small byproduct co-elutes with the starting material, but the intensity of the spots were examined at different times and the desired reaction was observed to be complete after ca. 12 min.



(70)

Following the same protocol as in eq 70, we simply reduced the reaction time to 12 min and observed 12% *E*-olefin **367** (eq 71). The reaction was complete after 12 minutes but some olefin isomerization was still occurring. Using less Cy_3SnH (1.5 equiv) resulted in recovered starting material after 12 min.



(71)

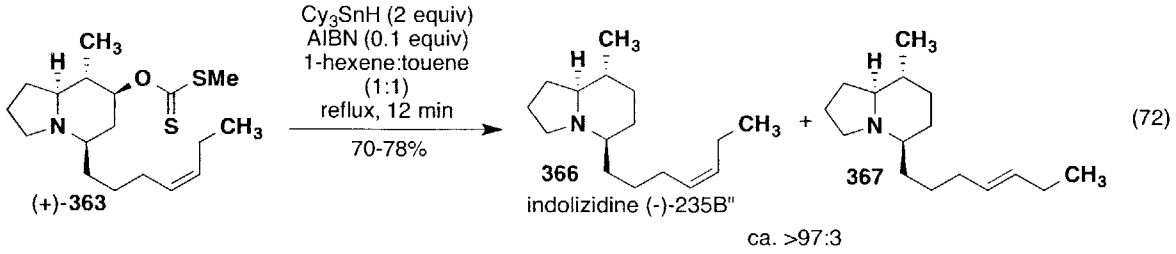
Using 2 equivalents of Cy_3SnH and catalytic AIBN in refluxing toluene for ca. 12 min consistently provided the desired product with <15% of the *E*-olefin. $AgNO_3$ impregnated silica gel is often used to separate carbon-carbon double bond isomers; however, attempts to separate the two products using $AgNO_3$-impregnated silica gel failed. We tried several methods for preparing $AgNO_3$/silica gel as reported in the literature.[139] Column fractions did contain different ratios of the two products; however, there was not clean separation of either isomer.

Instead of trying to separate the small amount of *E*-olefin product, we examined another method to suppress the isomerization. We initially thought that a molecule with a terminal olefin might react with tin radicals faster than the internal alkene of our own substrate. We decided to use readily available and inexpensive 1-hexene to suppress radical addition to our substrate. Addition of 1 equivalent of 1-hexene did not improve the result as ca. 12% of *E*-alkene **367** was observed. However, increasing the amount of 1-hexene to 10 and 15 equivalents did reduce the amount of isomerization to 5% and the desired product was obtained in 78% and 77% yield respectively. 1-Hexene was clearly playing a role in suppressing the isomerization.

Using a 1:1 mixture of 1-hexene and toluene as solvent provided indolizidine 235B" in excellent yield with only 2-3% of the isomerized olefin (eq 72). As expected, using 1-hexene as the solvent resulted in a longer reaction time due to the low boiling point, but only ca. 4% of the

[139] For the preparation of $AgNO_3$ impregnated silica gel, see: (a) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425-447. (b) Ruprah, P. K.; Cros, J-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, *18*, 3145-3152. (c) Li, T-S.; Li, J-T.; Li, H-Z. *J. Chromatogr. A* **1995**, *715*, 372-375.

trans-alkene was observed. A mixture of toluene and 1-hexene worked well to reduce the amount of *E*-alkene formed without increasing the reaction time. Under these conditions deoxygenation of **363** affords indolizidine (-)-235B" in 70-78% yield.[140]



(72)

The optical rotation of our synthetic indolizidine (-)-235B" was in good agreement with the synthetic indolizidines reported in the literature with regard to both magnitude and sign. Satake and Shimizu determined the enantiomeric purity of their natural product to be 98% ee by ^{1}H NMR analysis of an intermediate using a Eu(TFC)3(Tris[3-(trifluoromethylhydroxy-methylene)camphorato]-europium(III) derivative). Kibayashi synthesized the natural product from enantiomerically pure (*R*)-citronellol and his synthetic indolizidine 235B" is in good agreement with our sample. Early in Polnaiszek's synthesis, the enantiomeric purity of an intermediate was determined by NMR analysis while a chiral auxiliary was still present on the nitrogen. We determined the enantiomeric ratio by forming the (R)-BNPA salt of the indolizidines and analyzing the sample by ^{1}H NMR on a 500 MHz instrument.

The ^{1}H NMR data for our synthetic indolizidine (-)-235B" is compared to the data reported in the previous syntheses in Table 11 and Table 12. The isolation report of (+)-235B" does not list ^{1}H NMR data, and instead shows an image of the spectrum in agreement with ours. Other literature reports show good agreement with our synthetic indolizidine. The multiplet we

[140] Indolizidine (+)-235B" was synthesized following the same route ($[\alpha]^{24}_D$ +89.0 (*c* 1.0, MeOH)). Deoxygenation of (-)-**363** furnished (+)-235B" in 70 % yield contaminated with 3% *E*-olefin.

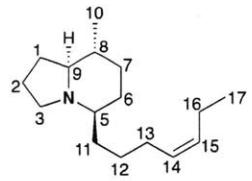
report at 0.90-0.99 ppm is overlooked in most literature reports. Most likely this proton is not reported because it overlaps with the triplet (3 H) from the terminal methyl group on the C8 substituent. Other groups assign this proton within the overlapping methylenes between 1.18 and 2.07 ppm.

The ^{13}C NMR data for our synthetic indolizidine 235B" is shown in Table 13 and is in good agreement with data reported in the previous syntheses as well as the sample isolated from nature. Several literature reports do not supply the reference for $CDCl_3$, possibly resulting in differences with the chemical shifts with our reported data.

Table 10. Comparison of optical rotation data for Indolizidine 235B".

This Work	(+)-235B" Tokuyama[102]	(-)-235B" Kibayashi[115]	(-)235B" Toyooka[119]	(-)-235B" Polniaszek[114]	(-)-235B" Comins[117]	(-)-235B" Shimizu[116]
$[\alpha]^{24}_D$ -90.0 (*c* 1.0, MeOH) $[\alpha]^{24}_D$ +89.0 (*c* 1.0, MeOH)	$[\alpha]$ +11.3 (*c* 1.0, MeOH)	$[\alpha]^{28}_D$ -85.4 (*c* 0.79, MeOH)	$[\alpha]^{26}_D$ -80.9(*c* 1.71, MeOH)	$[\alpha]_D$ -73.4 (*c* 1.0, MeOH)	$[\alpha]^{24}_D$ -88.0(*c* 1.0, MeOH)	$[\alpha]^{24}_D$ -72.0 (*c* 0.80, MeOH)

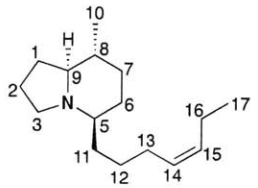
Table 11. Comparison of ^{1}H NMR data for Indolizidine 235B".



Indolizidine (-)-235B"

This Work (500 MHz, $CDCl_3$, 7.27 ppm)			(+)-235-B" Tokuyama[102] (500 MHz, $CDCl_3$)		(-)-235-B" Kibayashi[115] (400 or 500 MHz, $CDCl_3$, 7.26 ppm)		(-)-235B" Toyooka[119] (300 MHz, $CDCl_3$)	
Atom	**δ**	***J***	**δ**	***J***	**δ**	***J***	**δ**	***J***
10	0.86	d, *J* = 6.5 Hz, 3H	-	-	0.86	d, *J* = 6.5 Hz	0.85	d, *J* = 6.4 Hz, 3H
6	0.90-0.99	m, 1H	-	-	-	-	0.90-0.98	m, 1 H
17	0.95	t, *J* = 7.5 Hz, 3 H	-	-	0.95	t, *J* = 7.5 Hz, 3 H	0.96	t, *J* = 7.7 Hz, 3 H
3, 7, 8, 9, 12	1.18-1.51	m, 7 H	-	-	1.17-1.52	m, 8H	1.20-1.37	m, 5 H
1, 2, 6'	1.58-1.78	m, 5 H	-	-	1.56-1.79	m, 5H	1.41-1.55	m, 3 H
5, 11, 13, 16	1.82-2.07	m, 7 H	-	-	1.79-2.09	m, 7H	1.61-1.78	m, 5 H
			-	-			1.86-2.07	m, 6 H
3	3.25	td, *J* = 8.5, 1.5 Hz, 1 H	-	-	3.25	dt, *J* = 8.7, 1.8 Hz, 1H	3.28	t-like, *J* = 7.3 Hz, 1 H
14, 15	5.28-5.39	m, 2 H	-	-	5.27-5.39	m, 2H	5.29-5.39	m, 2H

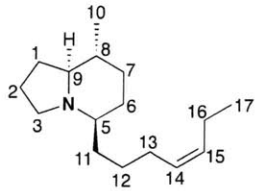
Table 12. Comparison of ^{1}H NMR data for indolizidine 235B".



Indolizidine (-)-235B"

This Work (500 MHz, $CDCl_3$, 7.27 ppm)			(-)-235B" Polniaszek[114] ($CDCl_3$)		(-)-235B" Comins[117] ($CDCl_3$, 300 MHz)		(+/-)-235B" Holmes[112] ($CDCl_3$, 250 MHz)	
Atom	**δ**	***J***	**δ**	***J***	**δ**	***J***	**δ**	***J***
10	0.86	d, J = 6.5 Hz, 3H	0.86	d, J = 6.5 Hz, 3H	0.87	d, J = 6.6 Hz, 3 H	0.83	d, J = 6.4 Hz, 3 H
6	0.90-0.99	m, 1H	-	-	-	-		-
17	0.95	t, J = 7.5 Hz, 3 H	0.94	t, J = 7.5 Hz, 3 H	0.95	t, J = 7.5 Hz, 3 H	0.92	t, J = 7.5 Hz, 3 H
3, 7, 8, 9, 12	1.18-1.51	m, 7 H	1.14-2.04	m, 16 H	1.14-1.55	m, 7 H	1.13-2.05	m, 20 H
1, 2, 6'	1.58-1.78	m, 5 H	-	-	1.55-1.80	m, 5 H		
5, 11, 13, 16	1.82-2.07	m, 7 H	-	-	1.80-2.10	m, 8 H		
3	3.25	td, J = 8.5, 1.5 Hz, 1 H	3.24	td, J = 8.5 Hz, 2.0 Hz, 1 H	3.26	dt, J = 1.8, 8.1 Hz, 1 H	3.28-3.20	td, J = 8.6, 2.2 Hz
14, 15	5.28-5.39	m, 2 H	5.24-5.48	m, 2 H	5.21-5.43	m, 2 H	5.24-5.39	m, 2 H

Table 13. Comparison of ^{13}C NMR data for indolizidine 235B".



Indolizidine (-)-235B"

	This Work[a] (125 MHz)	(+)-235B" Tokuyama[102] $CDCl_3$	(-)-235B" Kibayashi[b,115] $CDCl_3$	(-)-235B" Toyooka[119] $CDCl_3$, 75 MHz	(-)-235B" Polniaszek[114] $CDCl_3$	(-)-235B" Comins[117] $CDCl_3$, 75 MHz	(+/-)-235B" Holmes[112] $CDCl_3$, 100 MHz
Carbon	**δ**	**δ**	**δ**	**δ**	**δ**	**δ**	**δ**
1	29.3	29.1	29.2	29.0	29.1	29.1	29.00
2	20.6	20.4	20.5	20.4	20.4	20.4	20.29
3	52.1	51.8	52.0	51.8	51.9	51.8	51.80
5	63.7	63.4	63.6	63.6	63.5	63.4	63.42
6	31.5	31.3	31.4	31.1	31.3	31.3	31.16
7	33.9	33.7	33.9	33.7	33.8	33.7	33.62
8	36.8	36.5	36.7	36.4	36.7	36.6	36.49
9	71.6	71.3	71.5	71.4	71.4	71.4	71.33
10	19.1	18.8	19.0	19.0	19.0	18.9	18.96
11	34.5	34.2	34.4	34.1	34.3	34.3	34.14
12	26.2	25.9	26.1	26.1	26.0	26.0	25.94
13	27.6	27.4	27.5	27.4	27.5	27.4	27.36
14	129.2	128.9	129.1	128.8	129.0	129.0	128.90
15	132.0	131.7	131.9	131.7	131.8	131.8	131.77
16	20.8	20.5	20.6	20.6	20.6	20.5	20.5
17	14.6	14.3	14.5	14.5	14.4	14.3	14.4

[a] $CDCl_3$ was referenced to 77.23 ppm

[b] $CDCl_3$ was referenced to 77.1 ppm

Summary

Indolizidines (-)-235B', (+)-235B", and (-)-235B" have been synthesized from the same α-amino nitrile cycloadduct. The 10-step synthesis demonstrates the intramolecular [4 + 2] cycloaddition developed in our laboratory has the potential for accessing not only quinolizidine but also indolizidine alkaloids. The synthesis involves five high-yielding and straightforward steps to access the iminoacetonitrile substrate. The cycloaddition does provide a 70:30 mixture of enantiomers, however a diastereomeric salt resolution improves the er to >98:2. The substituents at C5 and C8 are set in the alkylation/reductive decyanation to be equatorial on the six-membered nitrogen-containing ring. To date, this is the most efficient route to indolizidines 235B' and 235B".

Part IV

Experimental Procedures

and

Spectra

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Diisopropylamine, N,N-diisopropylethylamine, triethylamine, ethanol, hexamethyldisilazane, and acetonitrile were distilled under argon from calcium hydride. *tert*-Butyldimethylsilyl trifluorometanesulfonate is distilled under vacuum immediately prior to use. Isoprene and 2-methyl-1,3-pentadiene was distilled under argon prior to use. *n*-Butyllithium was titrated according to the Watson-Eastham method using BHT in THF with 1,10-phenanthroline as an indicator.[1] N-Chlorosuccinimide was recrystallized from AcOH. Acetone-deactivated SiO_2 was prepared by mixing acetone with SiO_2 (ca. 10 mL/g) for 5 min, then using this slurry to build the column, followed by flushing the column with two column volumes of hexanes. 3-(*tert*-butyldimethylsiloxy)-1,3-pentadiene was prepared from 1-penten-3-one.[2] Dry $CeCl_3$ was prepared by drying $CeCl_3 \cdot 7H_2O$ under vacuum (ca. 0.1 mmHg) at 70 °C for 2 h, 100 °C for 3 h, then 140 °C for 16 h, and cooled at rt under argon. NaI was dried under vacuum (0.1 mmHg) at 70 °C for 24 h.

[1] (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-168. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209-213.
[2] Carreño, M. C.; Ruano, J. L. G.; Remor, C. Z.; Urbano, A. *Tetrahedron: Asymmetry*, **2000**, *11*, 4279-4296.

Molecular sieves (4 Å) were dried under vacuum (0.1 mmHg) at 300 °C for 16 h before use.[3] A NaOEt stock solution in ethanol was prepared by reacting freshly cut sodium pieces (ca. 0.5 cm^3) with dry ethanol in a 100-mL, three-necked, round bottom flask, equipped with rubber septum, glass stopper and reflux condenser fit with an argon inlet adapter. Ethyl iodide and methyl iodide were filtered through Al_2O_3 prior to use. The resulting solution was diluted to 100 mL using ethanol. Phosphoric acid diethyl ester 4-iodo-butyl ester was prepared from 1-iodo-4-butanol.[4] Tricyclohexyltin hyride was prepared following a literature procedure.[5]

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^1H NMR spectra were recorded on Varian Mercury 300 (300 MHz), Varian Inova 500 (500 MHz), Bruker Avance-400 (400 MHz), and Bruker Avance-600 (600 MHz) spectrometers. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR spectra were recorded on Varian Mercury 300 (75 MHz), Varian Inova 500 (125 MHz), and Bruker Avance-400 (100 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 tesla Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ or by Atlantic Microlab, Inc. of Norcross, GA.

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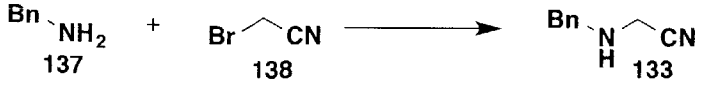
[3] 60 °C oven for up to two months without any noticeable effect on the reaction.
[4] Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745-2748.
[5] Jousseaume, B.; Lahcini, M.; Rascle, M.-C.; Ribot, F.; Sanchez, C. Organometallics, **1995**, *14*, 685-689

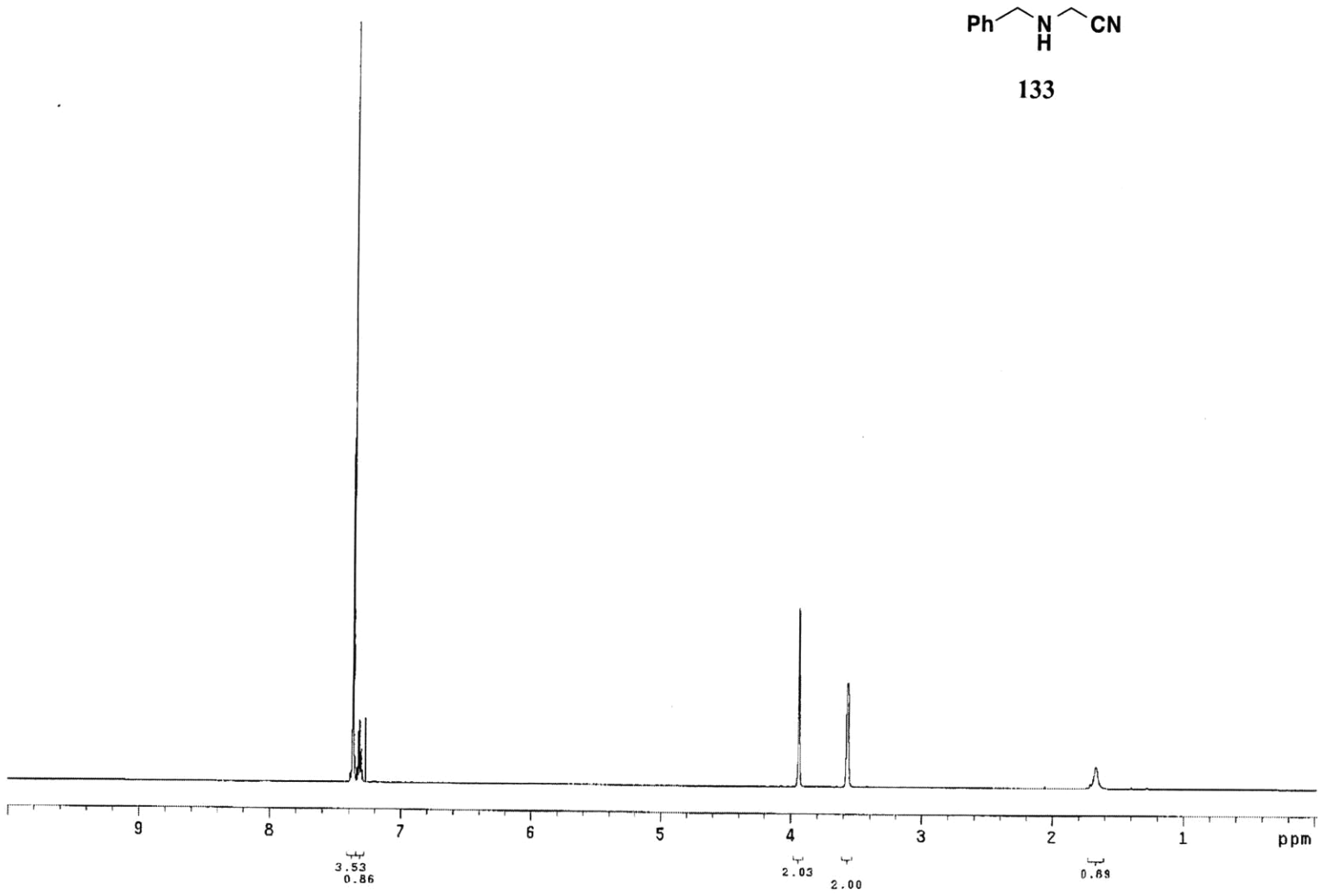
Intermolecular Cycloadditions of Iminoacetonitriles and Transformations:

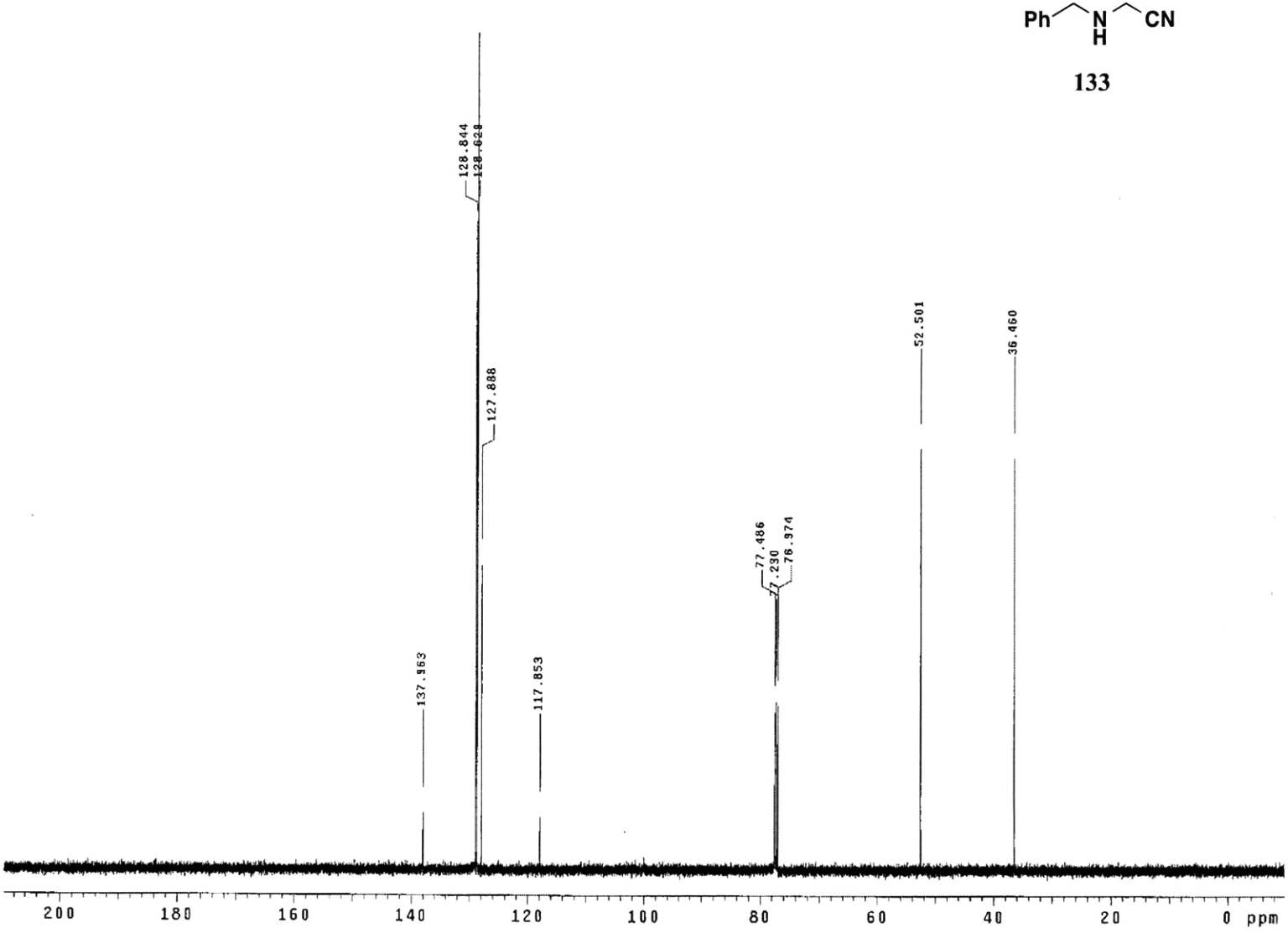
Experimentals and Spectra



N-Benzylaminoacetonitrile (133). A 250-mL, round-bottomed flask equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of benzylamine (3.80 mL, 3.73 g, 34.8 mmol, 1.0 equiv) and diisopropylethylamine (12.2 mL, 9.04 g, 69.6 mmol, 2.0 equiv) in 80 mL of CH_3CN. Bromoacetonitrile (2.35 mL, 4.17 g, 34.8 mmol, 1.0 equiv) was added dropwise via syringe over 2 min, and the resulting pale yellow reaction mixture was stirred at rt for 18 h. The reaction mixture was concentrated via rotary evaporation and the resulting residue was dissolved in 50 mL of CH_2Cl_2 and 50 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 100 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.986 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 20-35% EtOAc-hexanes) provided 4.950 g (97%) of **133** as a clear, colorless oil with spectral data consistent with the literature.[6] IR (thin film) 3332, 3064, 3030, 2928, 2845, 2234, 1958, 1604, 1496, 1455, and 1123 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.38 (m, 5 H), 3.94 (s, 2 H), 3.57 (d, J =3.5 Hz, 2 H), 1.67 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 128.8, 128.6, 127.9, 117.9, 52.5, 36.5; HRMS (m/z) $[M+H]^+$ calcd for $C_9H_{10}N_2$: 147.0917. Found: 147.0920.

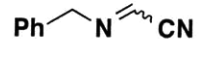
[6] Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis*, **2000**, 1299.


Ph
N
H
CN
133
9
8
7
6
5
4
3
2
1
ppm
3.53
0.86
2.03
2.00
0.89

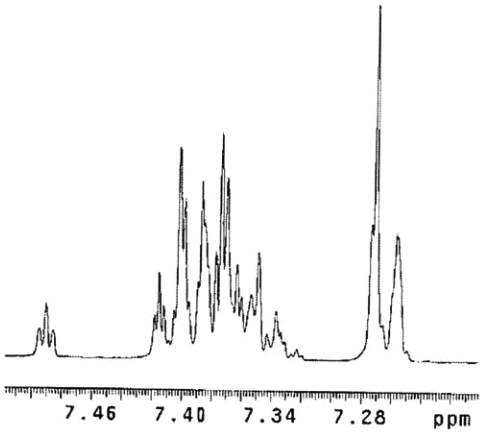

Ph
N
H
CN
133
128.844
128.628
127.888
137.963
117.853
77.486
77.230
76.974
52.501
36.460
200
180
160
140
120
100
80
60
40
20
0 ppm

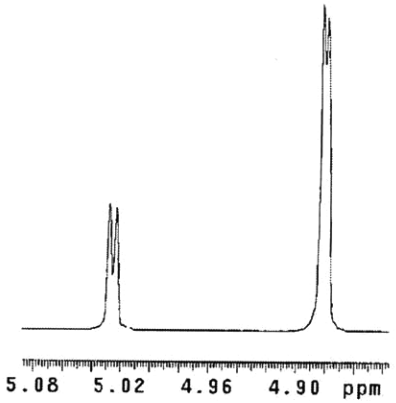
N-Benzyliminoacetonitrile (134). A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NCS (1.01 g, 7.52 mmol, 1.0 equiv) and 20 mL of THF. A solution of amine **133** (1.100 g, 7.524 mmol, 1.0 equiv) in 20 mL of THF was added over ca. 2 min via cannula and the reaction mixture was stirred at rt for 45 min. The resulting mixture was cooled at 0 °C while NaOEt (1.43 M in ethanol, 5.57 mL, 7.90 mmol, 1.05 equiv) was added dropwise via syringe over 10 min. The reaction mixture was stirred at 0 °C for 3 h and then diluted with 30 mL of water and 30 mL of diethyl ether. The aqueous layer was extracted with three 15-mL portions of ether, and the combined organic layers were washed with 30 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.151 g of an orange oil. Purification by column chromatography on 35 g of acetone-deactivated silica gel (elution with 5% EtOAc-hexanes) provided 0.870 g (81%) of **134** (72:28 mixture of E and Z imine isomers by ^{1}H NMR analysis) as a yellow oil: IR (thin film) 3226, 3065, 3033, 2906, 1622, 1496, 1454, and 1361 cm^{-1}. For E isomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.42 (m, 4 H), 7.27 (d, J = 8.5 Hz, 2 H), 4.88 (d, J = 1.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 135.6, 129.2, 128.6, 128.3, 114.7, 66.1; For Z isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (t, J = 2.3 Hz, 1 H), 7.33-7.43 (m, 5 H), 5.02 (d, J = 2.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 132.0, 129.0, 128.2, 128.1, 109.7, 63.6; HRMS (m/z) $[M+Na]^+$ calcd for $C_9H_8N_2$: 167.0580. Found: 167.0587.

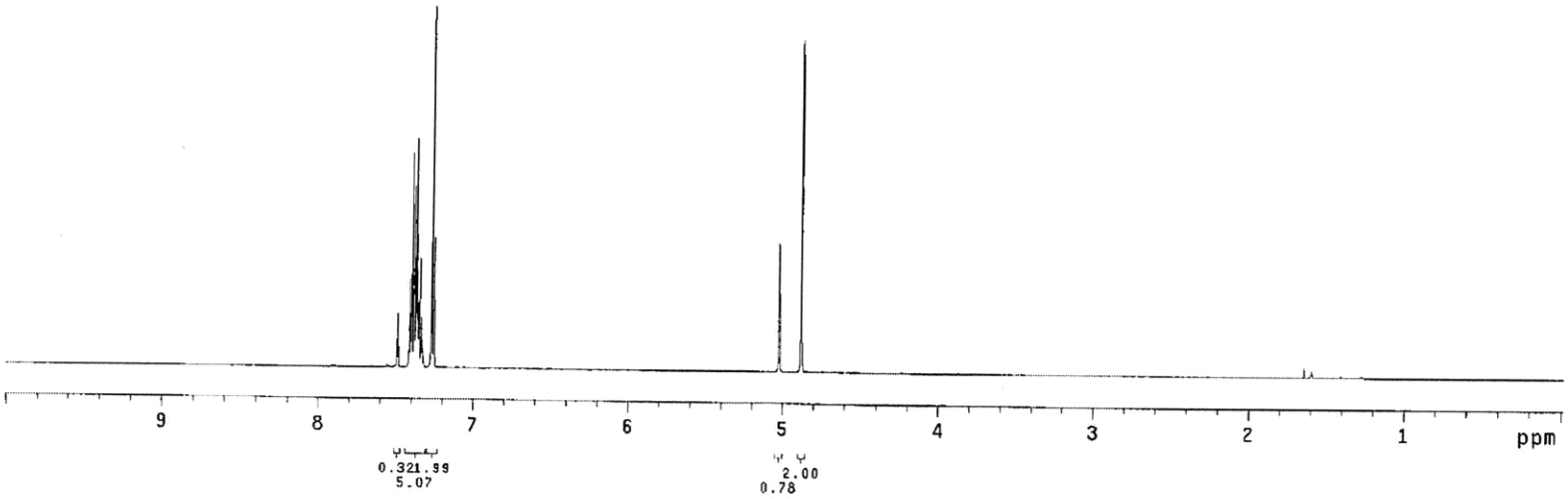
E/Z 72:28

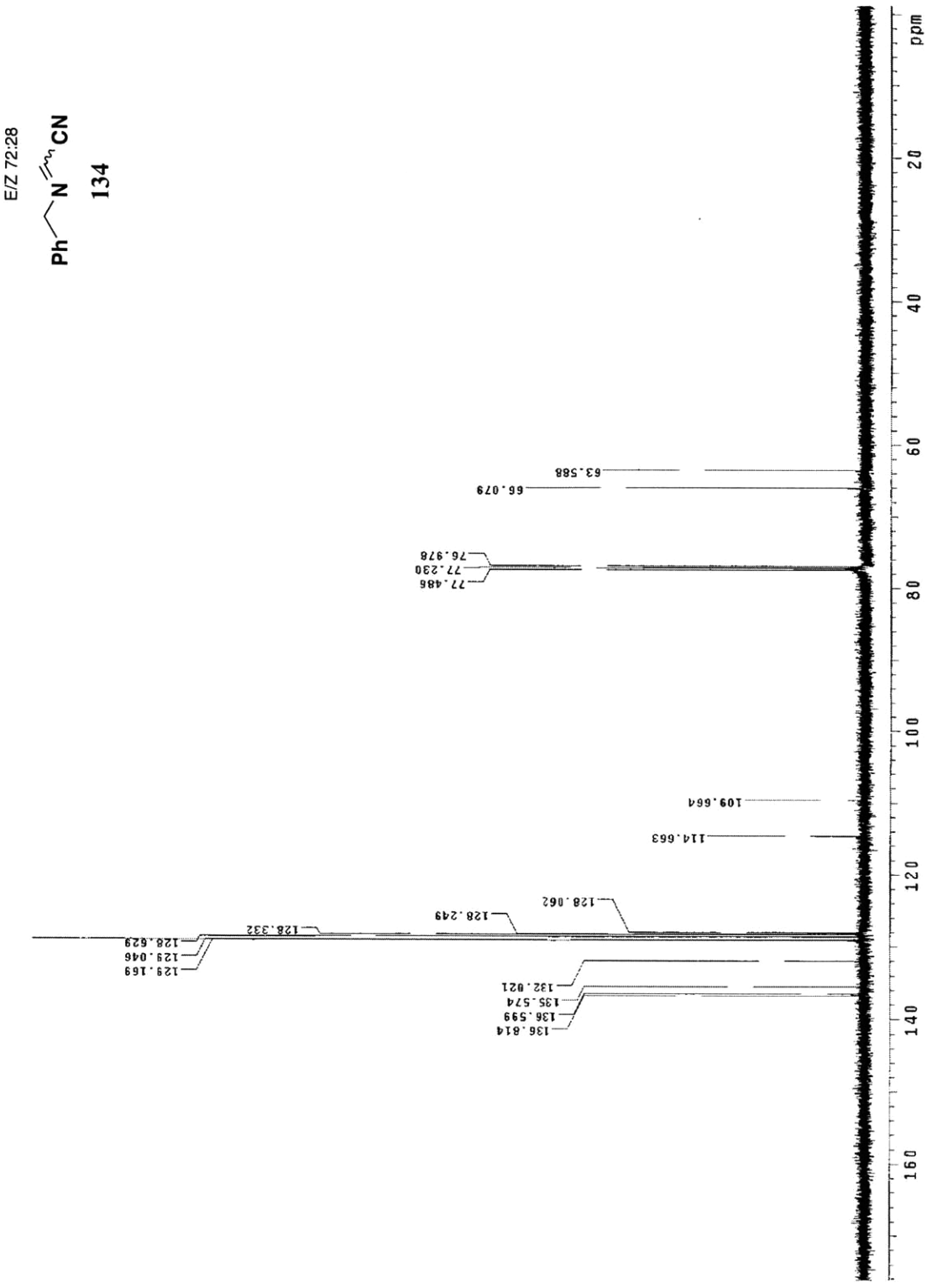

Ph
N
CN

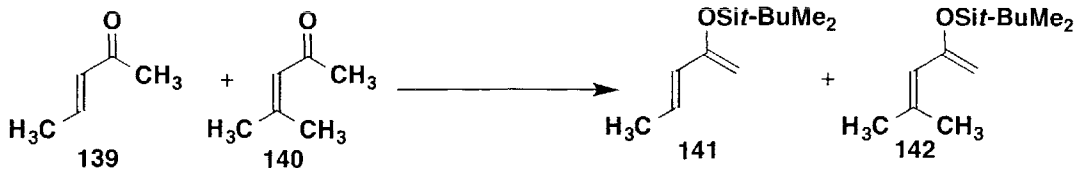
134


7.46
7.40
7.34
7.28
ppm


5.08
5.02
4.96
4.90
ppm


9
8
7
6
5
4
3
2
1
ppm
0.32
1.99
5.07
2.00
0.78

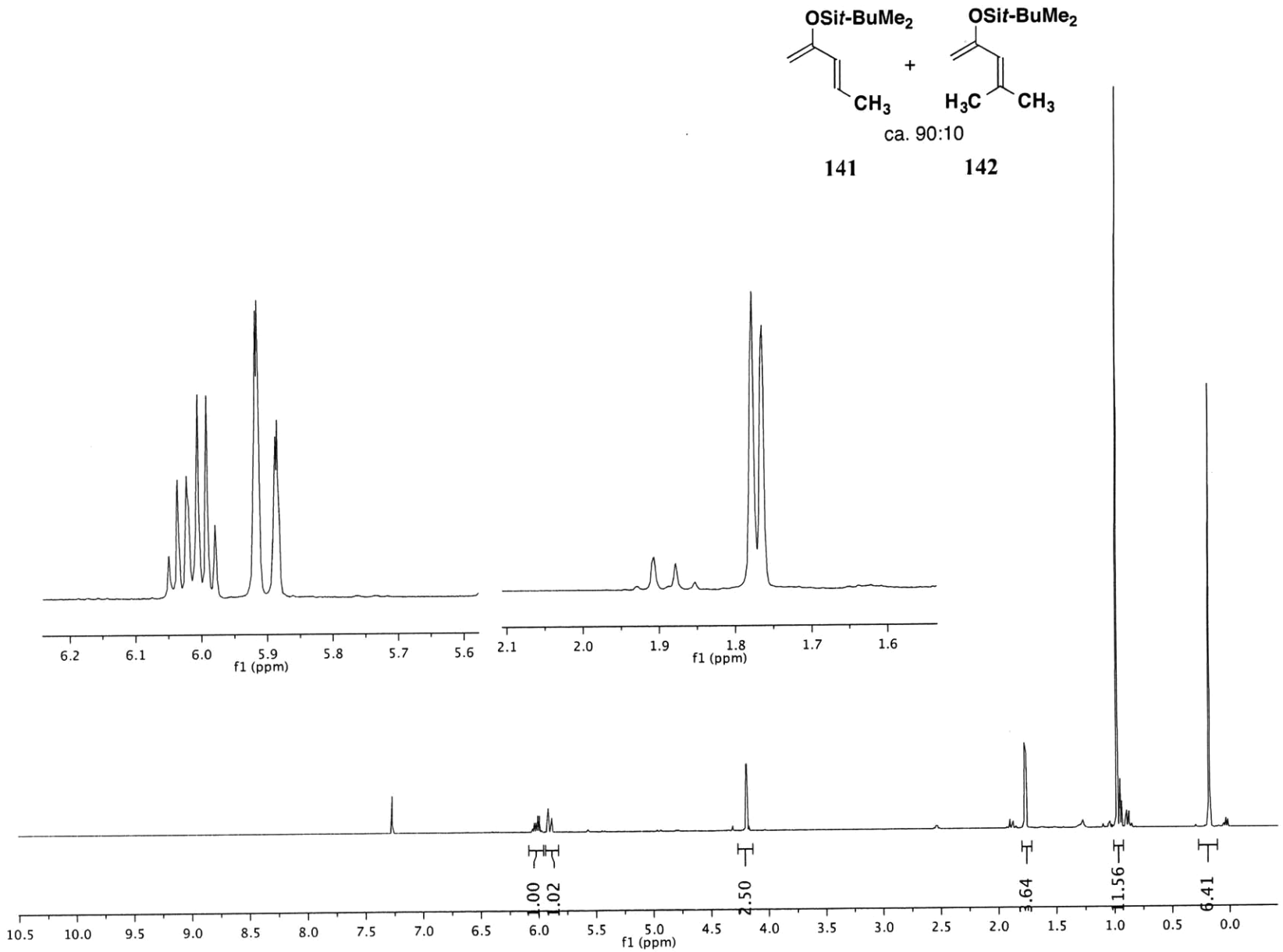

E/Z 72:28
Ph
N
CN
134
63.588
66.079
76.978
77.230
77.486
109.664
114.663
128.062
128.249
128.332
128.629
129.046
129.169
132.021
135.574
136.599
136.814
ppm
20
40
60
80
100
120
140
160

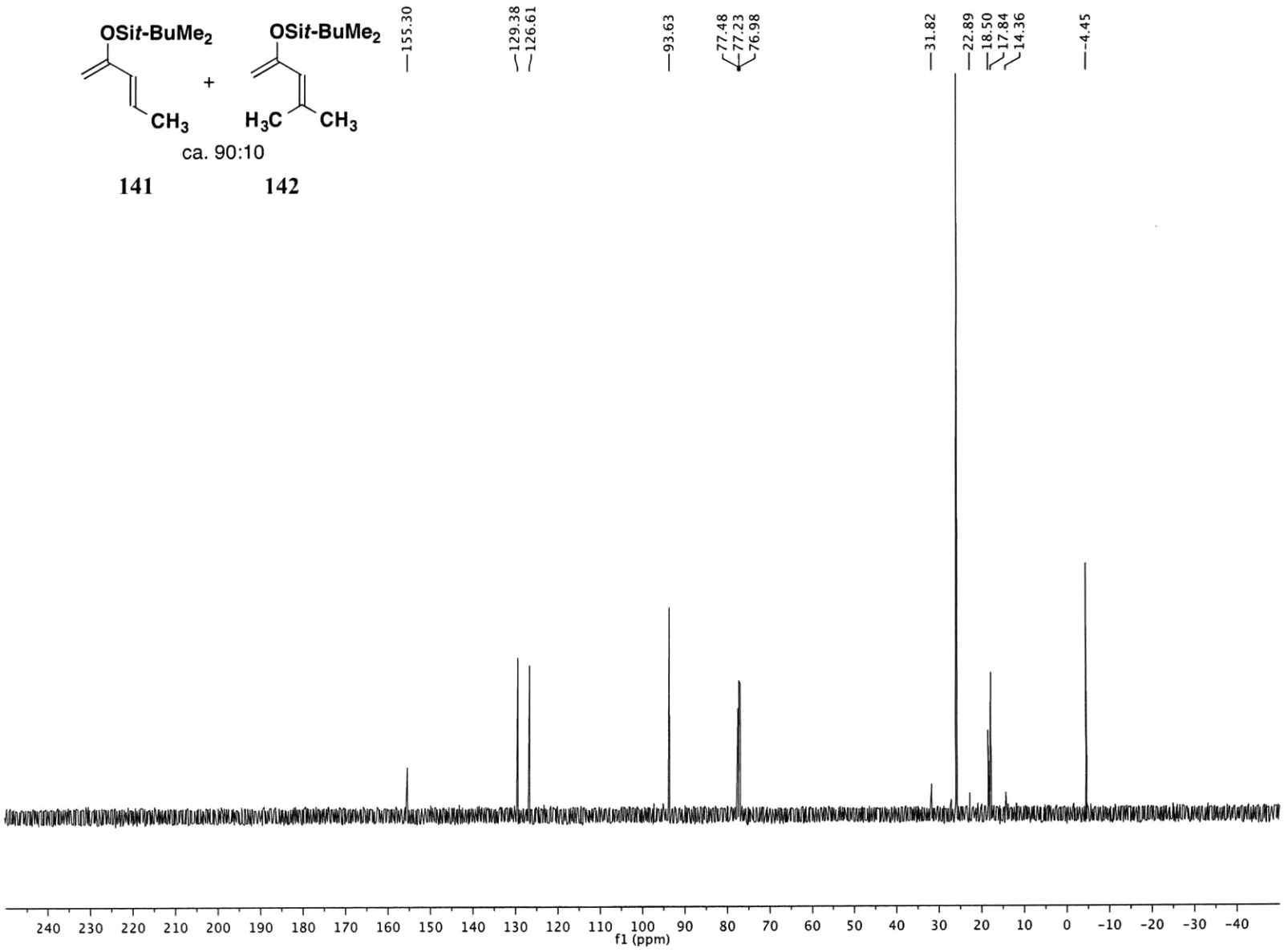


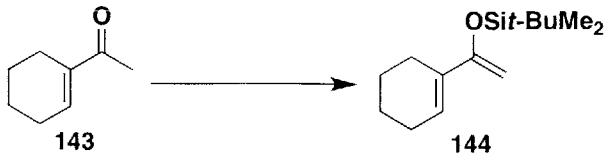
(*E*)-2-*tert*-Butyldimethylsiloxy-1,3-pentadiene (141).[7] A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with NaI (2.676 g, 17.85 mmol, 1.5 equiv), CH_3CN (30 mL), Et_3N (3.33 mL, 2.41 g, 23.8 mmol, 2.0 equiv), 3-penten-2-one (90% purity,[8] 1.16 mL, 1.00 g, 11.9 mmol, 1.0 equiv), and *tert*-butyldimethylsilyl chloride (1.79 g, 11.9 mmol, 1.0 equiv) and the resulting mixture was stirred at rt for 20 h in the dark. The reaction mixture was diluted with 30 mL of satd $NaHCO_3$ solution and 30 mL of ether. The aqueous layer was separated and extracted with three 30-mL portions of ether, and the combined organic layers were washed with 35 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 2.130 g of a dark red oil. Purification by column chromatography on 30 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 1.872 g of a 90:10 mixture of **141** and **142** (calculated yield of **141**: 79%) as a light yellow oil with spectral data consistent with that reported previously:[6] IR (thin film) 2931, 2886, 1657, 1593, 1319, 1023, and 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.01 (dq, J = 14.5, 6.5 Hz, 1 H), 5.90 (dq, J = 15.0, 1.6 Hz, 1 H), 4.20 (s, 1 H), 4.19 (s, 1 H), 1.77 (dm, J = 6.5 Hz, 3 H), 0.98 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 129.4, 126.6, 93.6, 26.0, 18.5, 17.8, -4.5.

[7] (a) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529-3530. (b) Liu, H-J.; Wang, D-X.; Kim, J. B.; Browne, E. N. C.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 899-912. (c) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485-2490.

[8] This commercial material is a 90:10 mixture of **139** and 4-methyl-3-penten-2-one (**140**). For this reaction, 1.16 mL of the mixture was used, which was calculated to contain 11.9 mmol of **139**.

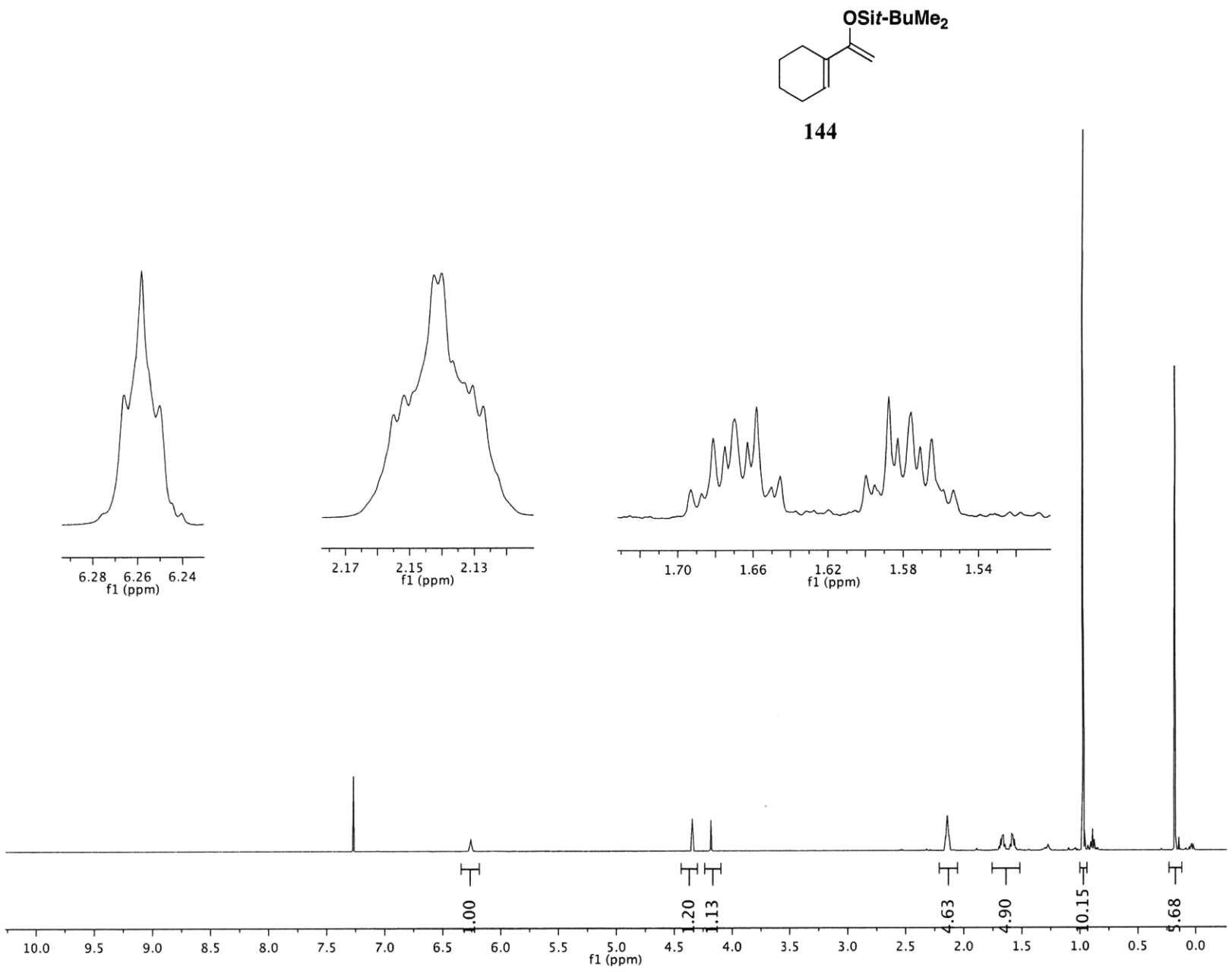

OSit-BuMe2
CH3
+
OSit-BuMe2
H3C
CH3
ca. 90:10
141
142
6.2
6.1
6.0
5.9
5.8
5.7
5.6
f1 (ppm)
2.1
2.0
1.9
1.8
1.7
1.6
f1 (ppm)
1.00
1.02
2.50
3.64
11.56
6.41
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

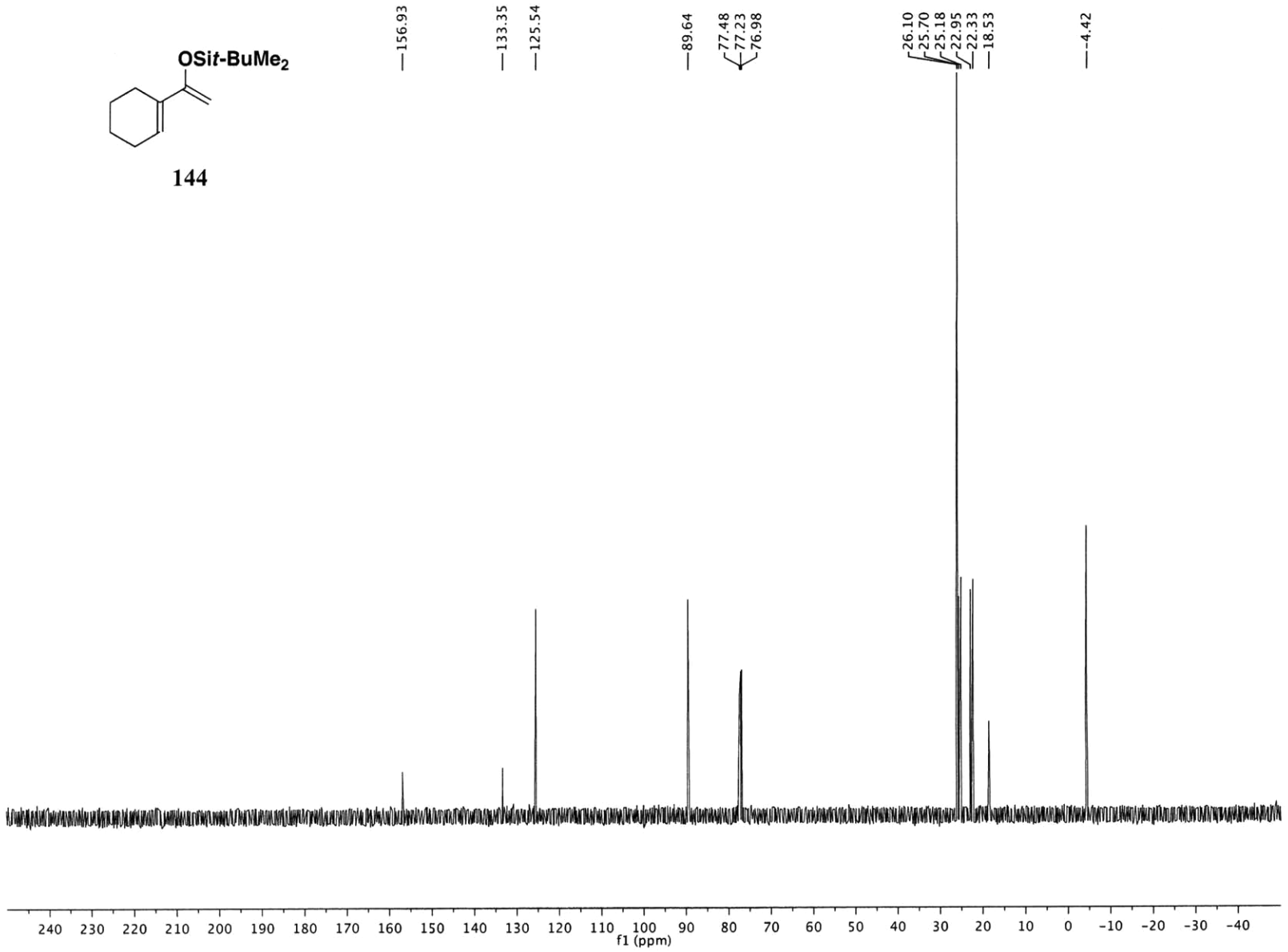

OSit-BuMe2
CH3
+
OSit-BuMe2
H3C
CH3
ca. 90:10
141
142
155.30
129.38
126.61
93.63
77.48
77.23
76.98
31.82
22.89
18.50
17.84
14.36
-4.45
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)



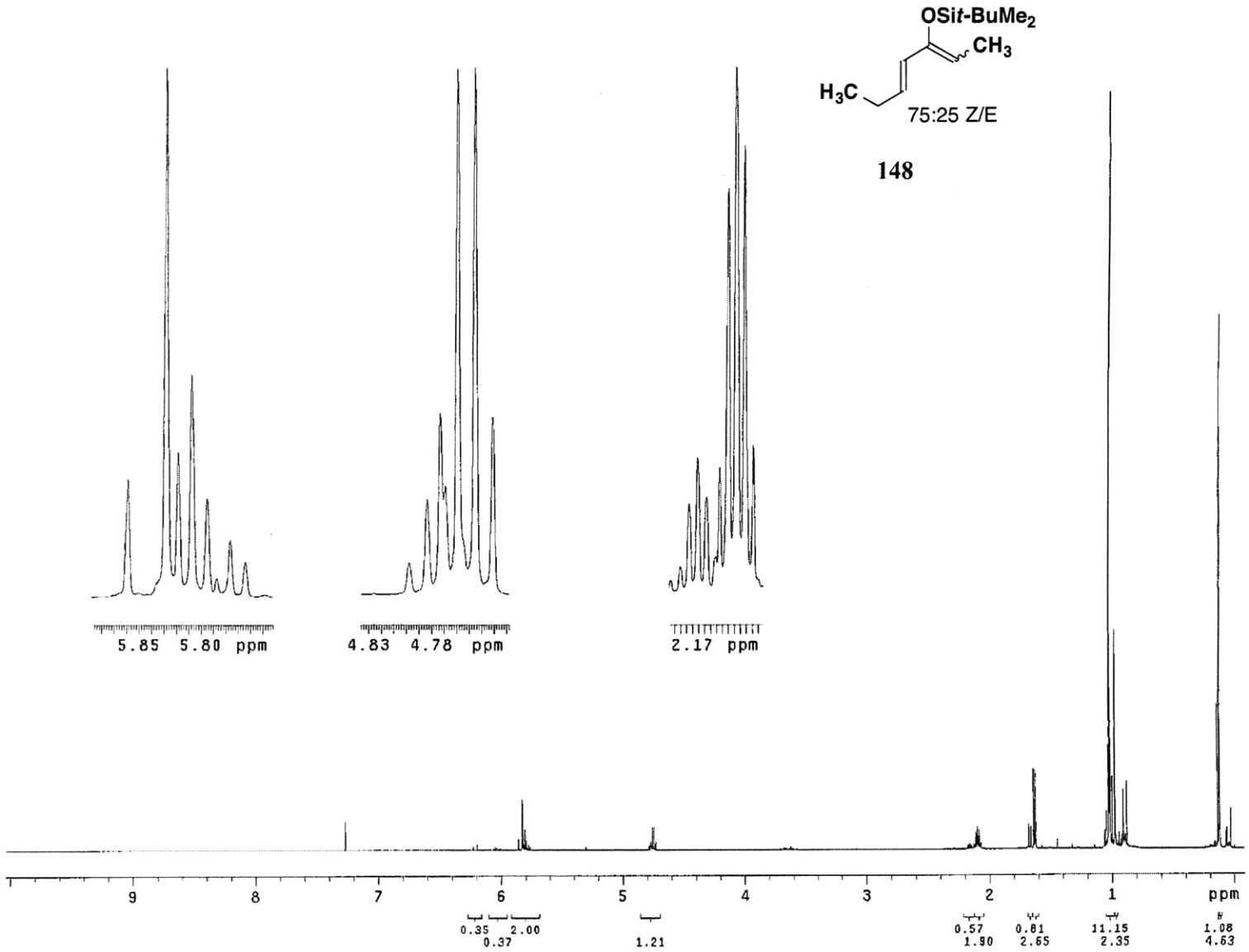
***tert*-Butyl((1-(cyclohex-1-en-1-yl)vinyl)oxy)dimethylsilane (144).**[9] A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with NaI (3.621 g, 24.15 mmol, 1.5 equiv), CH_3CN (50 mL), Et_3N (4.53 mL, 3.25 g, 32.2 mmol, 2.0 equiv), 1-acetylcyclohexene (2.08 mL, 2.00 g, 16.1 mmol, 1.0 equiv), and *tert*-butyldimethylsilyl chloride (1.317g, 16.10 mmol, 1.0 equiv) and the resulting mixture was stirred at rt for 18 h in the dark. The reaction mixture was diluted with 30 mL of satd $NaHCO_3$ solution and 30 mL of ether. The aqueous layer was separated and extracted with three 30-mL portions of ether, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 2.776 g of a dark red oil. Purification by column chromatography on 45 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 2.590 g (70%) of **144** as a light yellow oil with spectral data consistent with that reported previously:[5] IR (thin film) 2930, 1646, 1593, 1288, 1016, and 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (m, 1 H), 4.34 (s, 1 H), 4.18 (s, 1 H), 2.14 (m, 4 H), 1.67 (m, 2 H), 1.57 (m, 2 H), 0.97 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 133.4, 125.5, 89.6, 26.1, 25.7, 25.2, 22.9, 22.3, 18.5, -4.4.

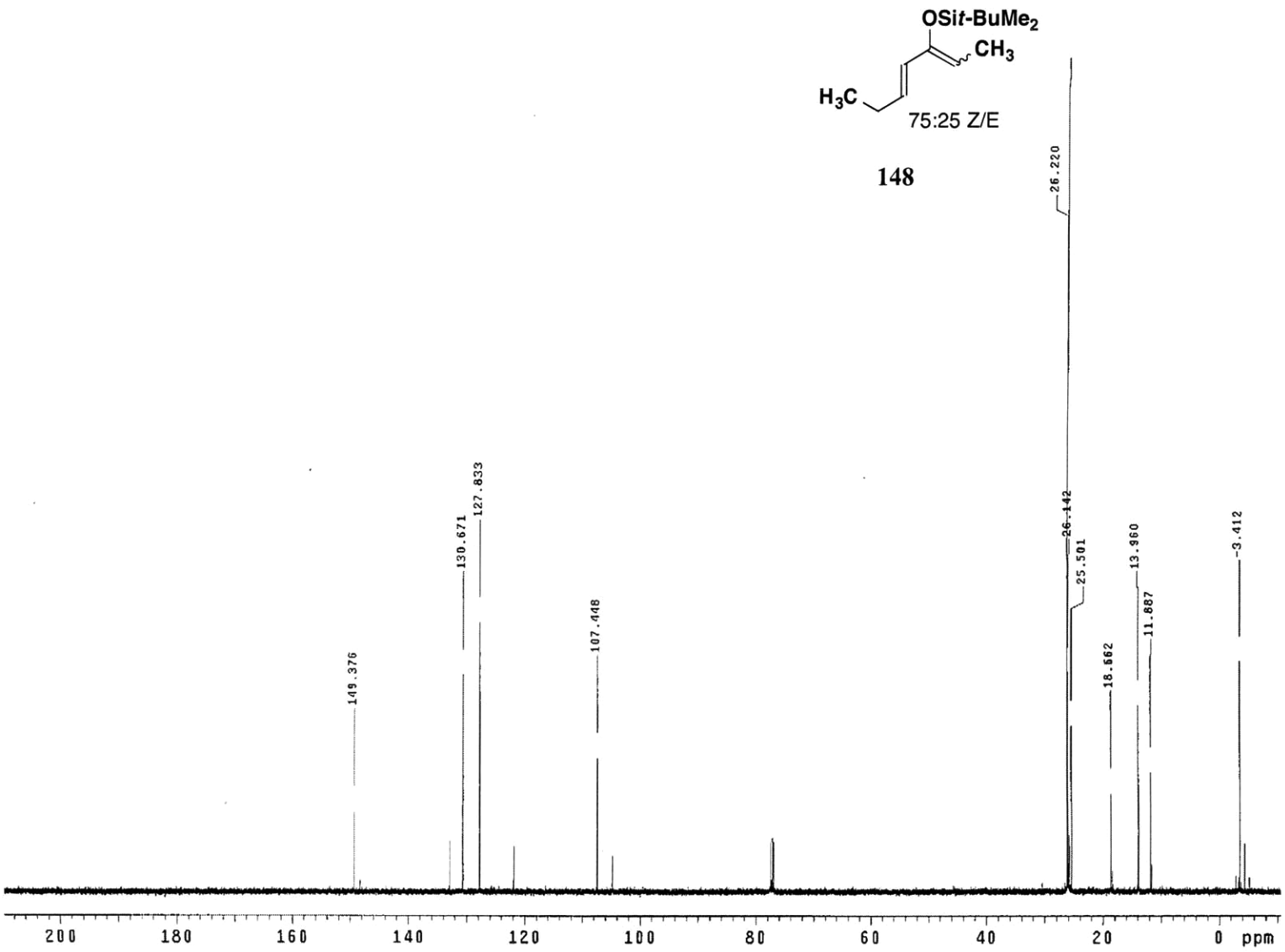
[9] For an alternate route to this diene see: Jung, M. E.; Nishimura, N. *Org. Lett.* **2001**, *3*, 2113-2115.

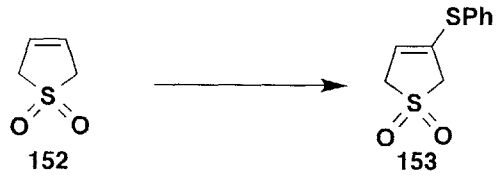

OSit-BuMe2
144
6.28 6.26 6.24
f1 (ppm)
2.17 2.15 2.13
f1 (ppm)
1.70 1.66 1.62 1.58 1.54
f1 (ppm)
1.00
1.20
1.13
4.63
4.90
10.15
5.68
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


OSit-BuMe2
144
156.93
133.35
125.54
89.64
77.48
77.23
76.98
26.10
25.70
25.18
22.95
22.33
18.53
-4.42
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

(*2Z,4E*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-heptadiene (148). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was changed with 5 mL of THF and diisopropylamine (0.760 mL, 0.549 g, 5.43 mmol, 1.5 equiv). The solution was cooled at 0 °C while *n*-BuLi solution (2.48 M in hexanes, 2.20 mL, 5.43 mmol, 1.5 equiv) was added dropwise via syringe over 5 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a solution of 4-hepten-3-one (0.406 g, 3.62 mmol, 1.0 equiv) in 5 mL of THF was added dropwise over 5 min. The resulting solution was stirred at -78 °C for 30 min, and then *t*-$BuMe_2SiOTf$ (1.25 mL, 1.44 g, 5.43 mmol, 1.5 equiv) was added dropwise over 4 min. The reaction mixture was allowed to warm to rt over 1 h, stirred at rt for 2 h, and then diluted with 10 mL of satd $NaHCO_3$ solution. The aqueous layer was extracted with three 15-mL portions of ether, dried over $MgSO_4$, filtered, and concentrated to give 1.440 g of a yellow oil. Purification by column chromatography on 50 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 1.060 g (86%) of **148** (75:25 mixture of Z/E isomers) as a light yellow oil: IR (thin film) 2960, 2931, 1628, 1473, 1254, 1041, 840, and 779 cm^{-1}; For *Z* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.76-5.86 (m, 2 H), 4.75 (q, J = 7.0 Hz, 1 H), 2.16 (m, 1 H), 2.09 (m, 1 H), 1.63 (d, J = 7.0 Hz, 3 H), 1.02 (s, 9 H), 1.01 (t, J = 7.0 Hz, 3 H), 0.12 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 130.7, 127.8, 107.4, 26.2, 25.5, 18.7, 14.0, 11.9, -3.4; HRMS (m/z) $[M+H]^+$ calcd for $C_{13}H_{26}OSi$: 227.1826. Found: 227.1833.

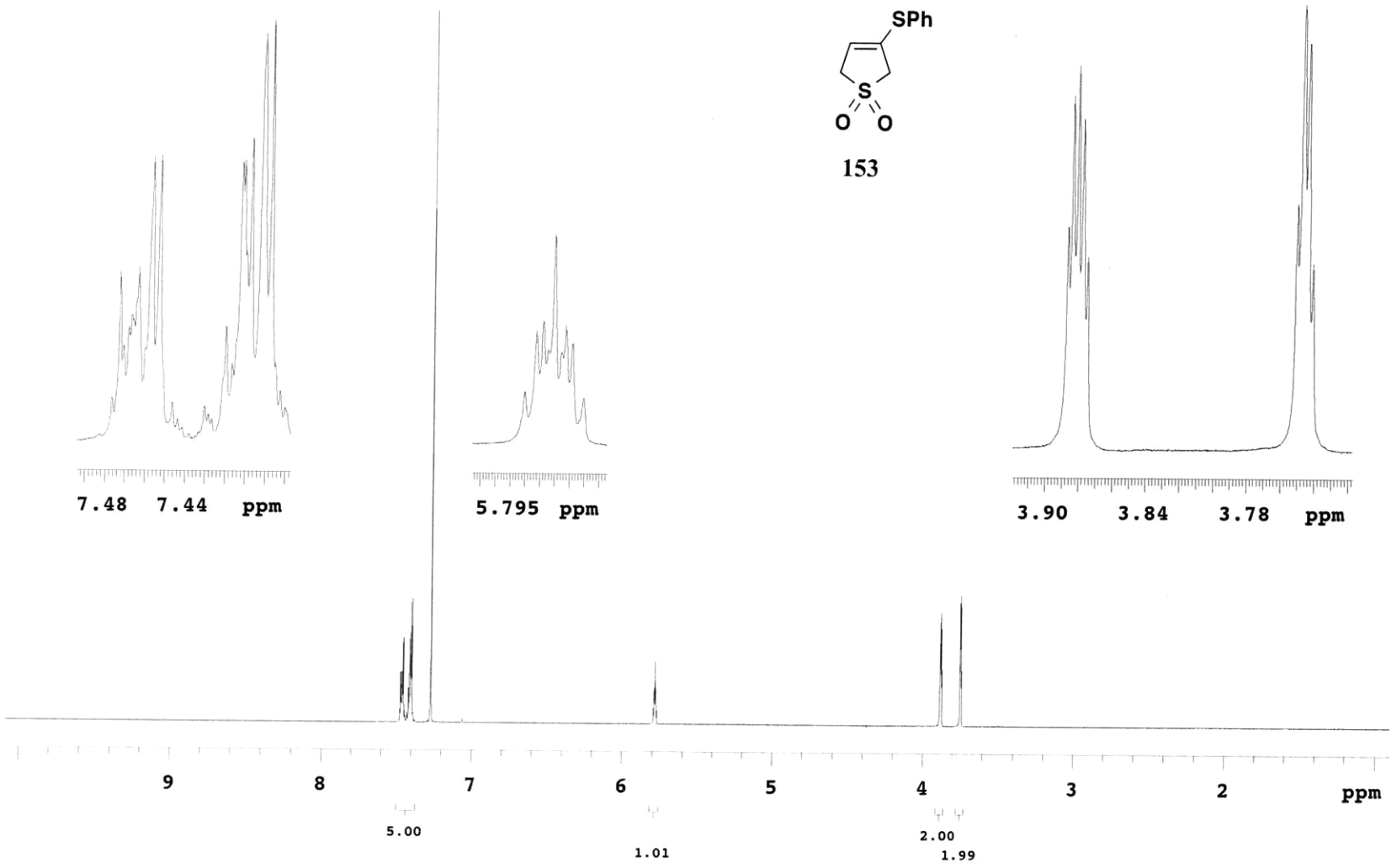

OSit-BuMe2
CH3
H3C
75:25 Z/E
148
5.85 5.80 ppm
4.83 4.78 ppm
2.17 ppm
9
8
7
6
5
4
3
2
1
ppm
0.35 2.00
0.37
1.21
0.57
1.90
0.81
2.65
11.15
2.35
1.08
4.63

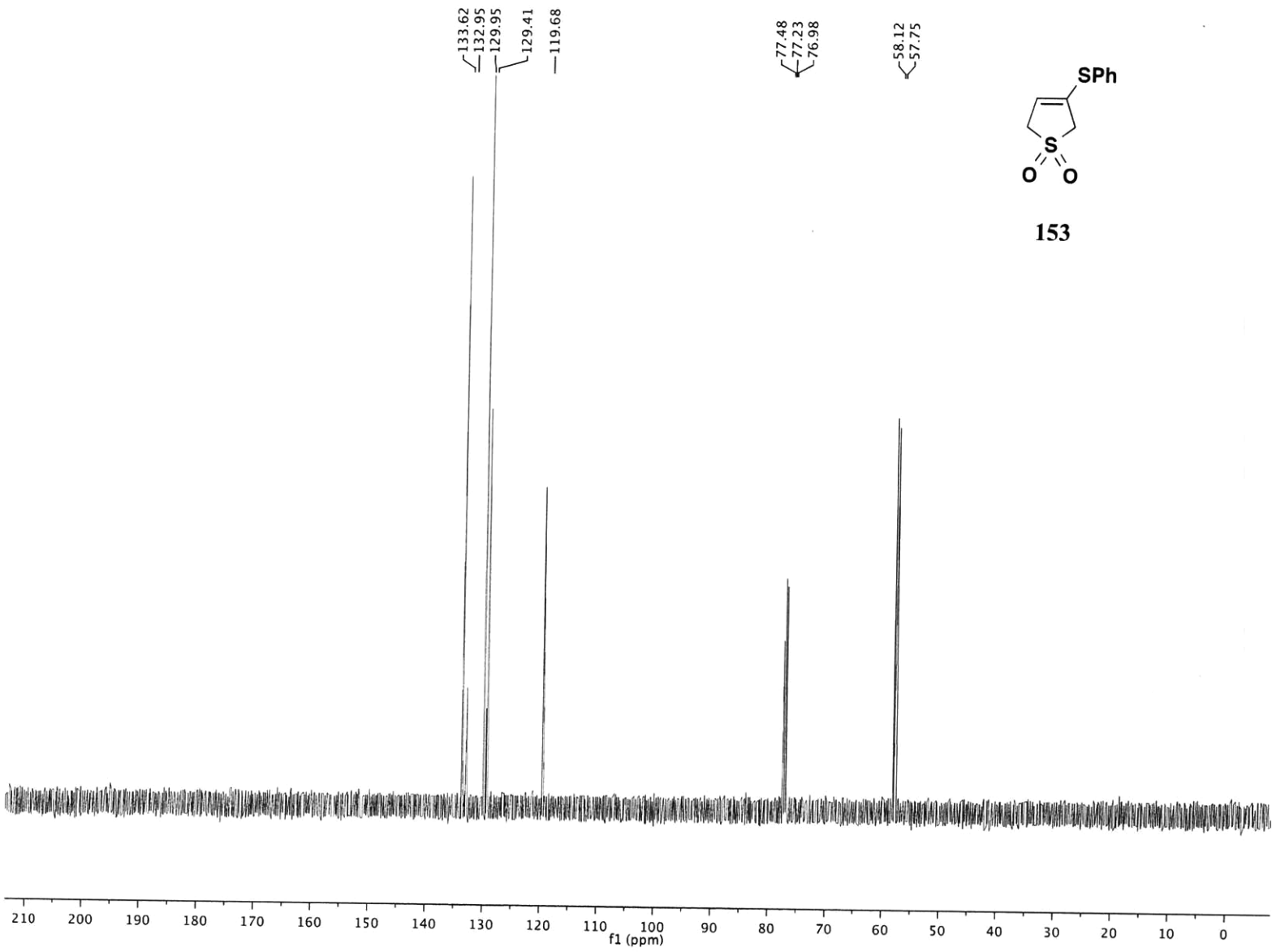

OSit-BuMe2
CH3
H3C
75:25 Z/E
148
149.376
130.671
127.833
107.448
26.220
26.142
25.501
18.662
13.960
11.887
-3.412
200
180
160
140
120
100
80
60
40
20
0 ppm

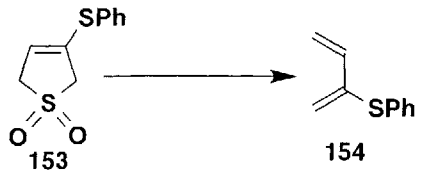


3-Phenylthio-2,5-dihydrothiophene 1,1-Dioxide (153).[10] A freshly prepared solution of benzenesulfenyl chloride[10] (15.0 mmol, 1.0 M solution in CH_2Cl_2, 1.0 equiv) prepared in a 50-mL, 2 necked, round bottomed flask complete with a reflux condenser, argon inlet adapter, and rubber septum was charged with 2,5-dihydrothiophene 1,1-dioxide (1.772 g, 15.00 mmol, 1.0 equiv) in one portion. The resulting solution was stirred at rt for 40 h and then Et_3N (3.14 mL, 2.04 g, 22.5 mmol, 1.5 equiv) was added dropwise over 5 min and the reaction mixture was stirred for 24 h at rt. The reaction mixture was then diluted with 70 mL of Et_2O. The organic layer was washed sequentially with 100 mL of H_2O, two 20-mL portions of 1 N HCl, 50 mL satd $NaHCO_3$ solution, and 16 mL satd NaCl solution. The aqueous $NaHCO_3$ and NaCl washes were combined and extract with 50 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to form 3.405 g of a yellow solid. The solids were quickly washed with a 50% Et_2O-hexanes mixture that was cooled at 0 °C and filtered to give 2.471 g (73%) of **153** as a white solid. IR (thin film) 3059, 2976, 1581, 1477, 1316, 1132, and 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.48 (m, 5 H), 5.78 (m, 1 H), 3.88 (m, 2 H), 3.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 133.0, 130.0, 129.6, 129.4, 119.7, 58.1, 57.7; HRMS (m/z) $[M+H]^+$ calcd for $C_{10}H_{10}O_2S_2$: 227.0195. Found: 227.0192.

[10] Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

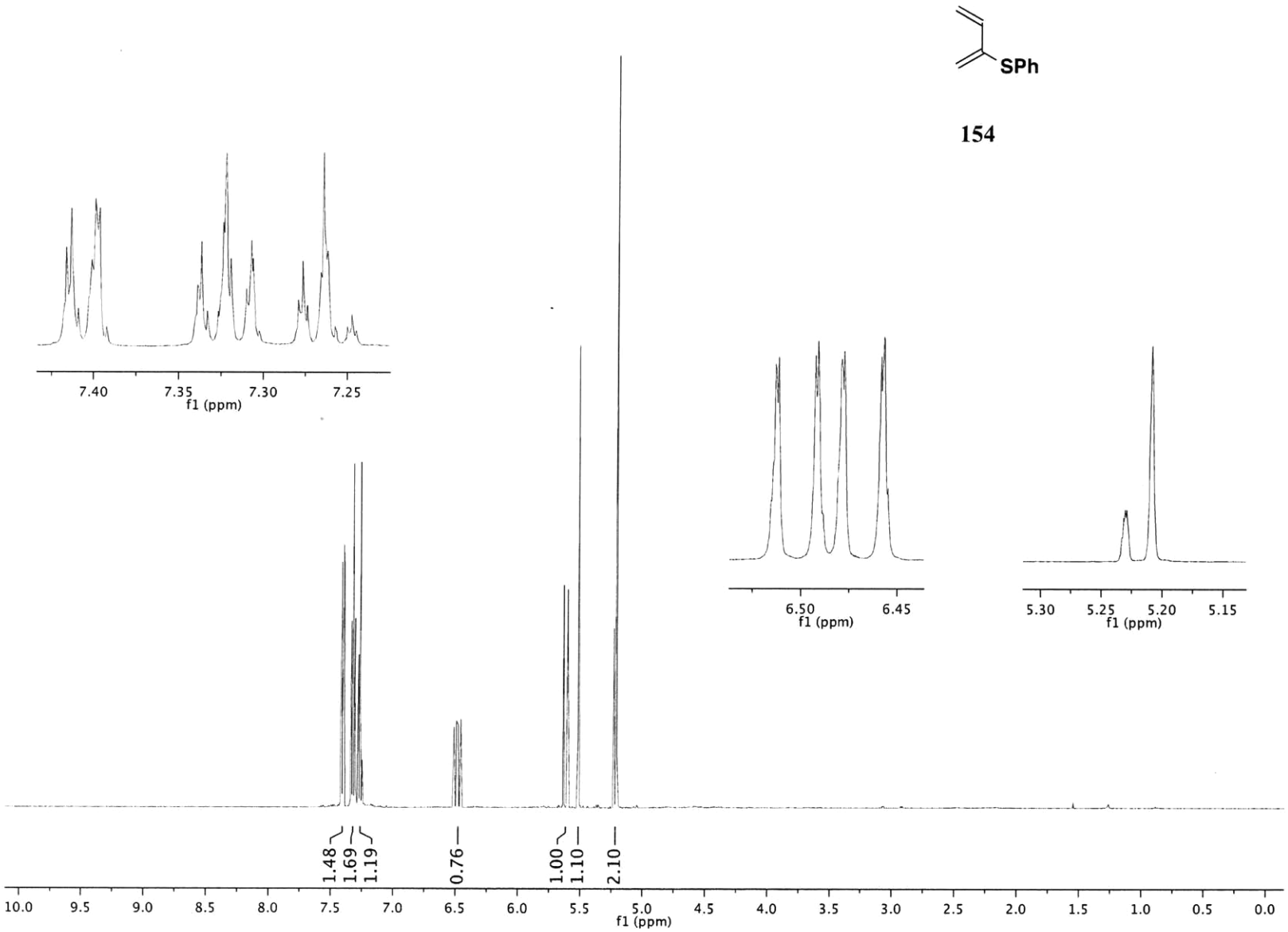

SPh
S
O
O
153
7.48
7.44
ppm
5.795
ppm
3.90
3.84
3.78
ppm
9
8
7
6
5
4
3
2
ppm
5.00
1.01
2.00
1.99


133.62
132.95
129.95
129.41
119.68
77.48
77.23
76.98
58.12
57.75
SPh
S
O
O
153
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

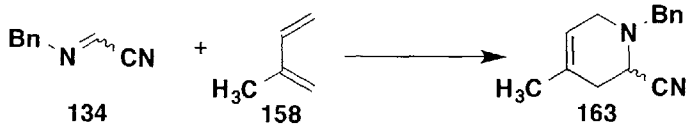


2-(Phenylthio)-1,3-butadiene (154).[11] A 100-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with 3-phenylthio-2,5-dihydrothiophene 1,1-dioxide (1.440 g, 6.36 mmol, 1.0 equiv), hydroquinone (0.014 g, 1.27 mmol, 0.02 equiv), $NaHCO_3$ (0.534 g, 6.36 mmol, 1.0 equiv), and 25 mL of toluene. The reaction mixture was stirred for 5 h at 110 °C, cooled at rt and concentrate to give a yellow semisolid. Purification by column chromatography on 35 g of silica gel (elution with hexanes) afforded 0.780 g (76%) of **154** as a colorless oil. IR (thin film) 3058, 1583, 1477, 1439, 742, and 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2 H), 7.30-7.34 (m, 2 H), 7.25-7.28 (m, 1 H), 6.48 (dd, J = 16.5, 10.5 Hz, 1 H), 5.62 (d, J = 17.0 Hz, 1 H), 5.51 (s, 1 H), 5.22 (d, J = 12.0 Hz, 1 H), 5.21 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 135.9, 133.7, 132.0, 129.3, 127.5, 120.0, 117.6; HRMS (m/z) $[M+H]^+$ calcd for $C_{10}H_{10}S$: 163.0576. Found: 163.0583.

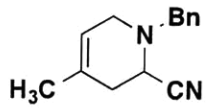
[11] Procedure adapted from: Chou, S-S. P.; Hung, C-C. *Synth. Commun.* **2001**, *31*, 1097


SPh
154
7.40
7.35
7.30
7.25
f1 (ppm)
6.50
6.45
f1 (ppm)
5.30
5.25
5.20
5.15
f1 (ppm)
1.48
1.69
1.19
0.76
1.00
1.10
2.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

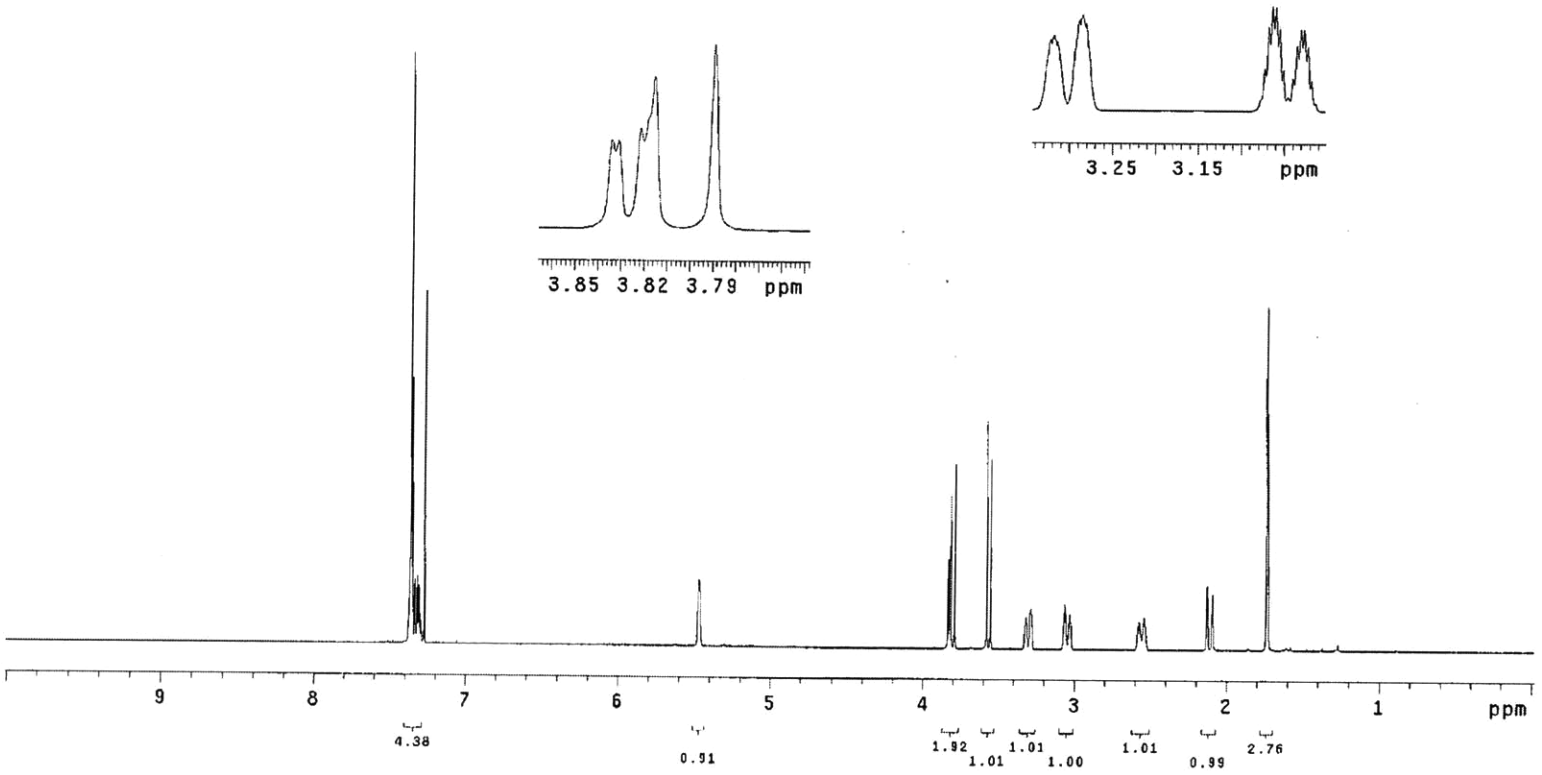
142.120
135.882
133.657
132.002
129.295
127.474
119.950
117.588
77.483
77.230
76.976
SPh
154
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

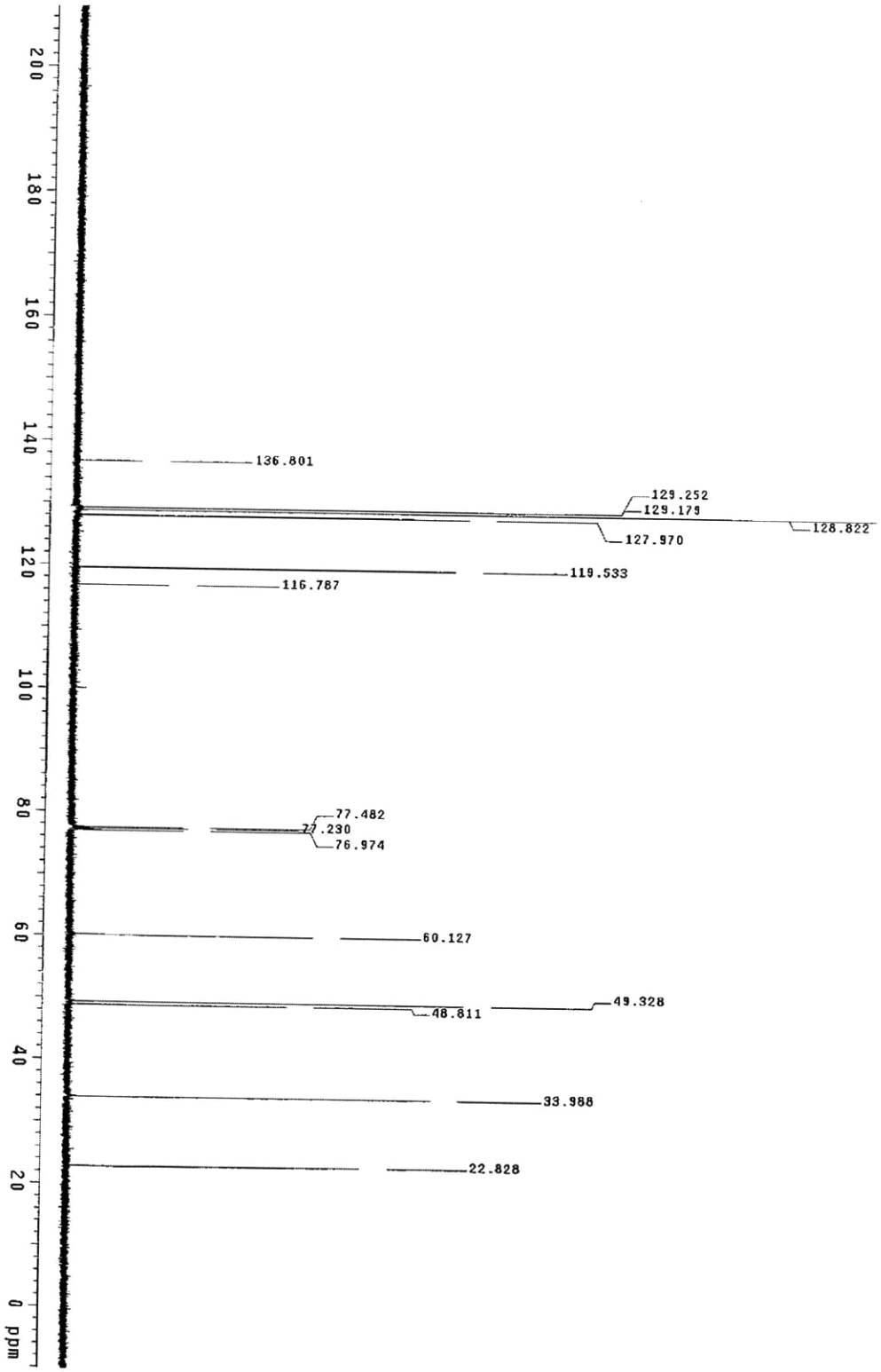


1-Benzyl-2-cyano-4-methyl-1,2,3,6-tetrahydropyridine (163). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.060 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.117 g, 0.810 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. The solution was cooled at -78 °C and isoprene (0.320 mL, 0.221 g, 3.24 mmol, 4.0 equiv) was added in one portion via syringe. Methanesulfonic acid (0.73M in CH_2Cl_2, 1.66 mL, 0.117 g, 1.22 mmol, 1.5 equiv) was then added dropwise over 2 min such that the internal temperature did not rise above -70 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.166 g of a yellow oil. Purification by column chromatography on 8 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.146 g (85%) of **163** as a colorless oil: IR (thin film) 3027, 2932, 1603, 1496, 1453, 1383, and 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.38 (m, 5 H), 5.47 (d, J = 2.3 Hz, 1H), 3.83 (dd, J = 5.5, 1.0 Hz, 1 H), 3.80 (d, J = 13.5 Hz, 1 H), 3.57 (d, J = 13.0 Hz, 1 H), 3.30 (dm, J = 15.5 Hz, 1 H), 3.04 (dm, J = 16.5 Hz, 1 H), 2.56 (dm, J = 15.0 Hz, 1 H), 2.11 (d, J = 17.0 Hz, 1 H), 1.73 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 129.3, 129.2, 128.8, 128.0, 119.6, 116.8, 60.1, 49.3, 48.8, 34.0, 22.9; HRMS (m/z) $[M+H]^+$ calcd for $C_{14}H_{16}N_2$: 213.1386. Found: 213.1389.

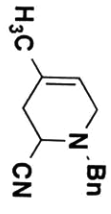

Bn
N
H_3C
CN

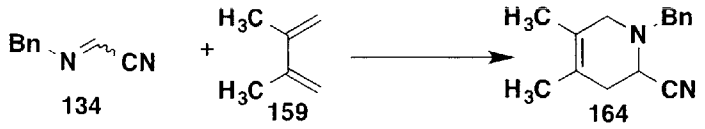
163


3.85 3.82 3.79 ppm
3.25 3.15 ppm
9
8
7
6
5
4
3
2
1
ppm
4.38
0.91
1.92
1.01
1.01
1.00
1.01
0.99
2.76

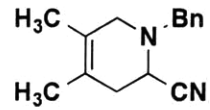

200
180
160
140
120
100
80
60
40
20
0 ppm
136.801
129.252
129.179
128.822
127.970
119.533
116.787
77.482
77.230
76.974
60.127
49.328
48.811
33.988
22.828

163

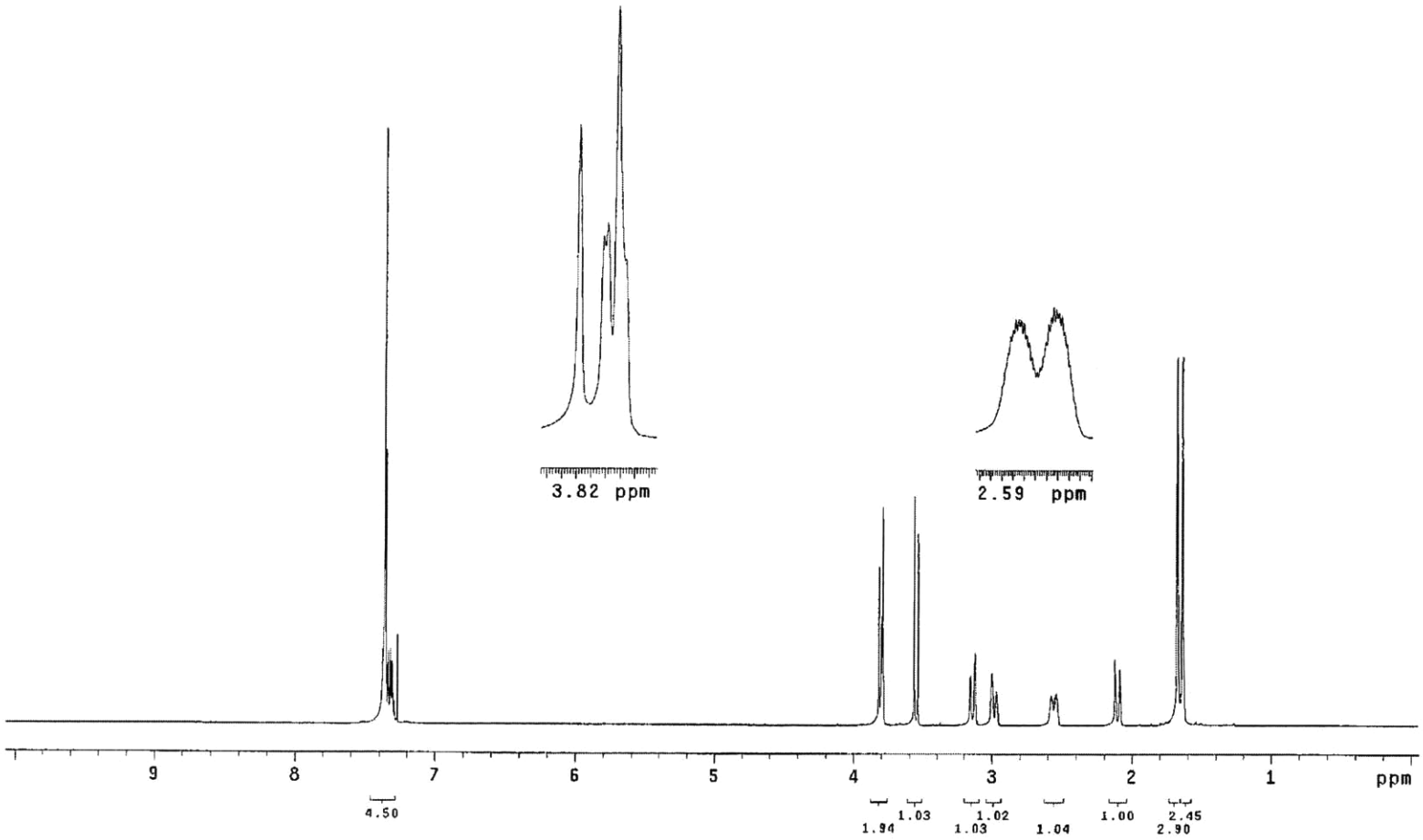

H3C
N
Bn
CN



1-Benzyl-2-cyano-4,5-dimethyl-1,2,3,6-tetrahydropyridine (164). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.100 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.107 g, 0.742 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. The solution was cooled at -78 °C and 2,3-dimethylbutadiene (0.336 mL, 0.244 g, 2.97 mmol, 4.0 equiv) was added in one portion via syringe. Methanesulfonic acid (0.73 M in CH_2Cl_2, 1.51 mL, 0.117 g, 1.11 mmol, 1.5 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -72 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.183 g of a yellow oil. Purification by column chromatography on 8 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.161 g (95%) of **164** as a yellow oil: IR (thin film) 2915, 2763, 2353, 2331, 2216, 1495, 1453, 1361, 1162, and 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.39 (m, 5 H), 3.80 (d, J = 13.0 Hz, 1 H), 3.79 (dd, J = 6.5, 1.0 Hz, 1 H), 3.55 (d, J = 13.0 Hz, 1 H), 3.14 (d, J = 16.0 Hz, 1 H), 2.98 (d, J = 16.0 Hz, 1 H), 2.56 (d, J = 14.5 Hz, 1 H), 2.10 (d, J = 17.0 Hz, 1 H), 1.67 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 129.3, 128.8, 128.0, 124.5, 121.3, 117.0, 60.1, 54.2, 49.2, 35.0, 18.3, 16.6; HRMS (m/z) $[M+H]^+$ calcd for $C_{15}H_{18}N_2$: 227.1543. Found: 227.1548.


H3C
N
Bn
H3C
CN

164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2.59 ppm
9
8
7
6
5
4
3
2
1
ppm
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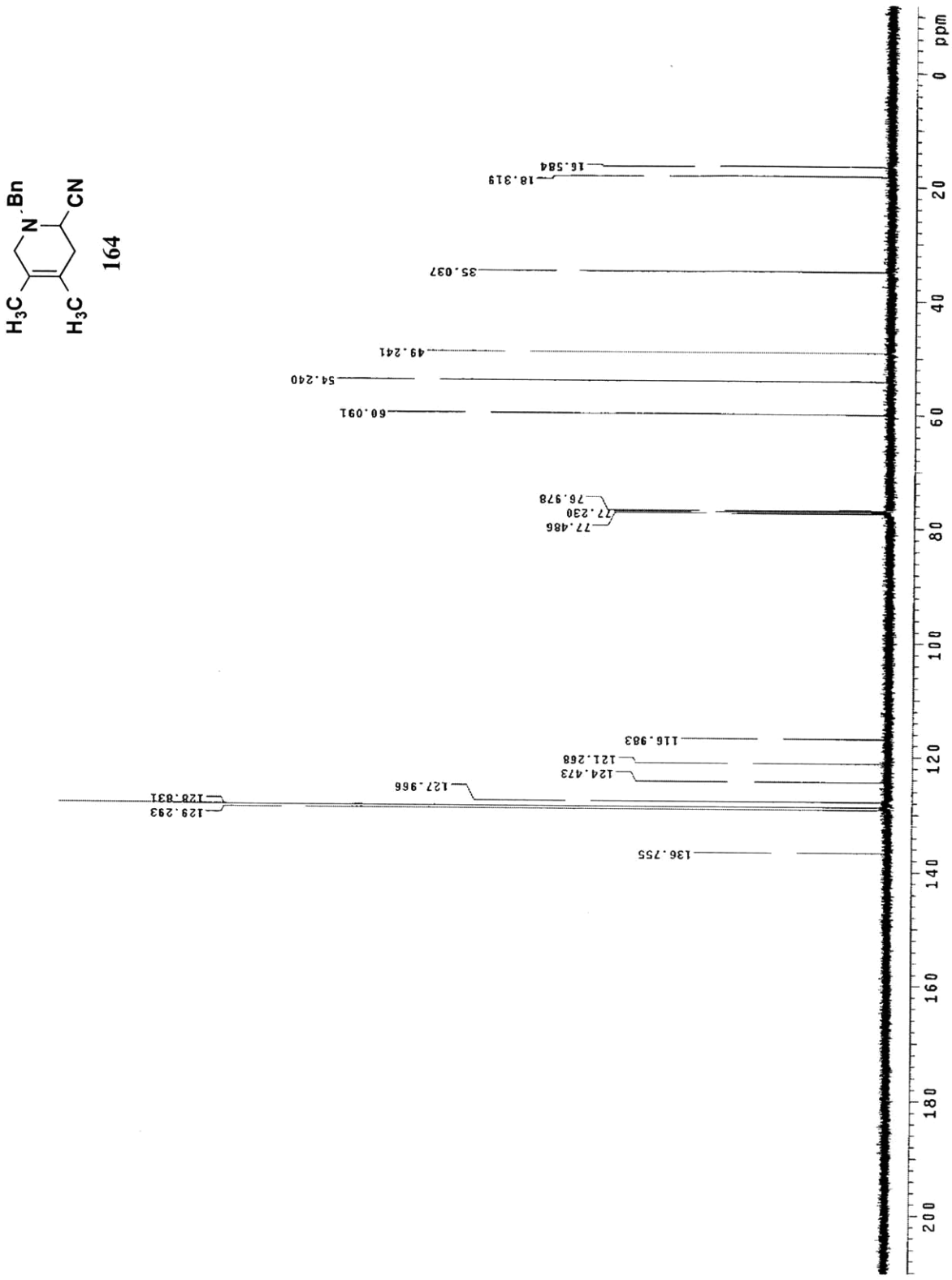
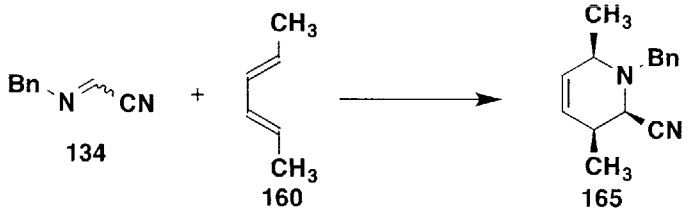
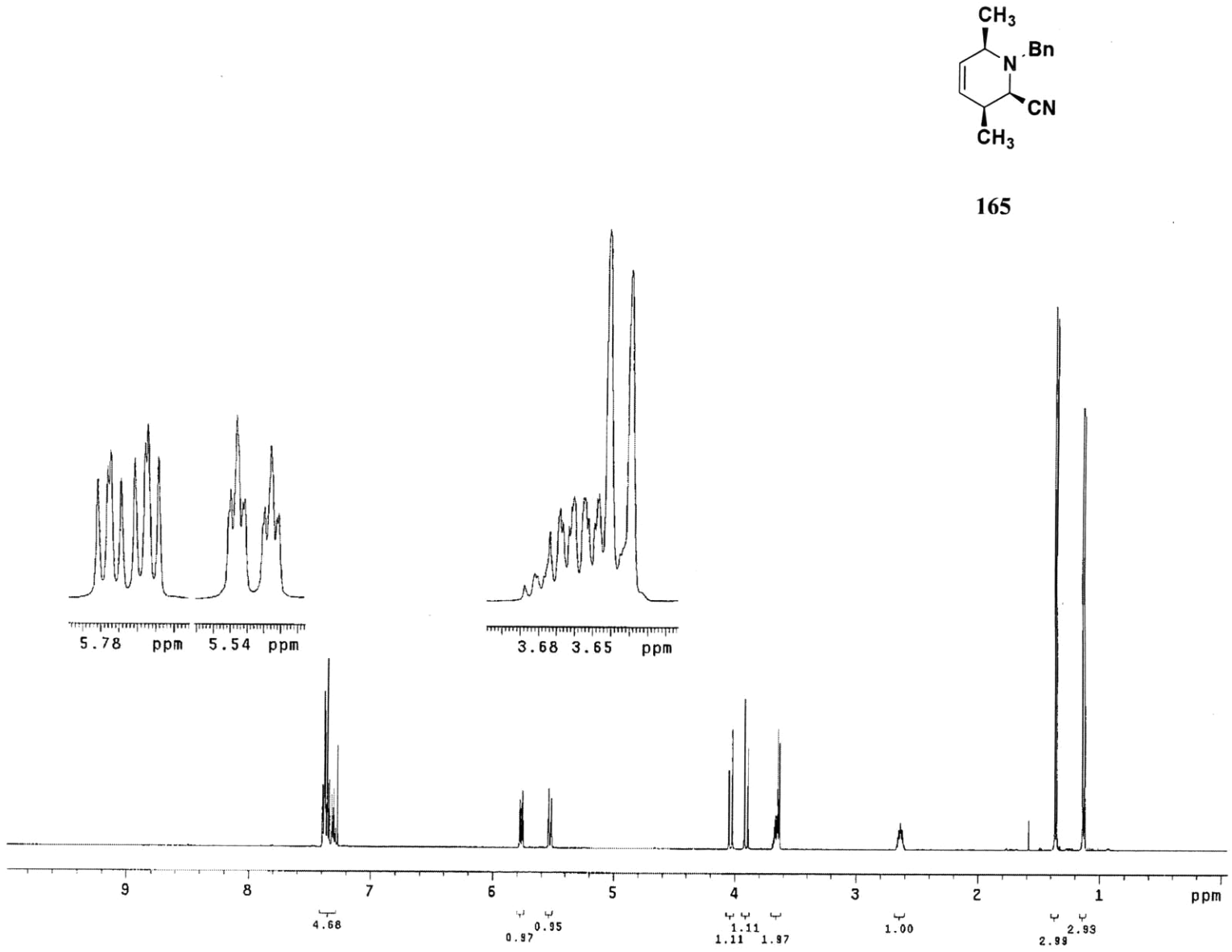
1.03
1.03
1.02
1.04
1.00
2.90
2.45


Bn
N
CN
H3C
H3C
164
16.584
18.319
35.037
49.241
54.240
60.091
76.978
77.230
77.486
116.983
121.268
124.473
127.966
128.831
129.293
136.755
0
20
40
60
80
100
120
140
160
180
200
ppm



1-Benzyl-2-cyano-3,6-dimethyl-1,2,3,6-tetrahydropyridine (165). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.060 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.121 g, 0.840 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. The solution was cooled at -78 °C and 2,4-hexadiene (0.380 mL, 0.276 g, 3.36 mmol, 4.0 equiv) was added in one portion via syringe. Methanesulfonic acid (0.73 M in CH_2Cl_2, 1.72 mL, 0.121 g, 1.26 mmol, 1.5 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -68 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.152 g of a yellow oil. Purification by column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.135 g (71%) of **165** as a colorless oil: IR (thin film) 3030, 2877, 2960, 2877, 1722, 1495, 1454, 1379, 1326, 1149, and 1121 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5 H), 5.76 (dt, J = 10.0, 2.5 Hz, 1 H), 5.52 (dt, J = 10.0, 2.0 Hz, 1 H), 3.97 (AB q, J = 14.0 Hz, 2 H), 3.63-3.69 (m, 1 H), 3.63 (d, J = 5.5 Hz, 1 H), 2.60-2.67 (m, 1 H), 1.36 (d, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 131.4, 128.9, 128.8, 127.8, 126.9, 119.5, 56.3, 53.0, 50.8, 32.4, 17.5, 14.9; HRMS (m/z) $[M+H]^+$ calcd for $C_{15}H_{18}N_2$: 227.1543. Found: 227.1550.


CH3
Bn
N
CN
CH3
5.78 ppm 5.54 ppm
3.68 3.65 ppm
9
8
7
6
5
4
3
2
1
ppm
4.68
0.97
0.95
1.11
1.11
1.97
1.00
2.99
2.93

165

CH3
N
Bn
CN
CH3
165
137.670
131.381
128.877
128.780
127.787
126.936
119.492
77.482
77.230
76.974
56.296
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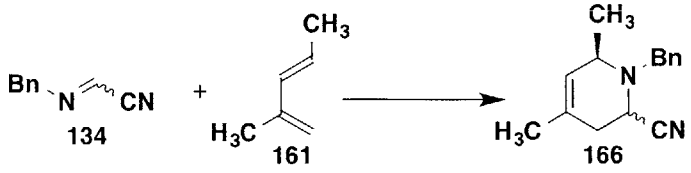
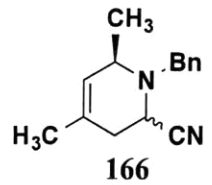
180
160
140
120
100
80
60
40
20
0 ppm

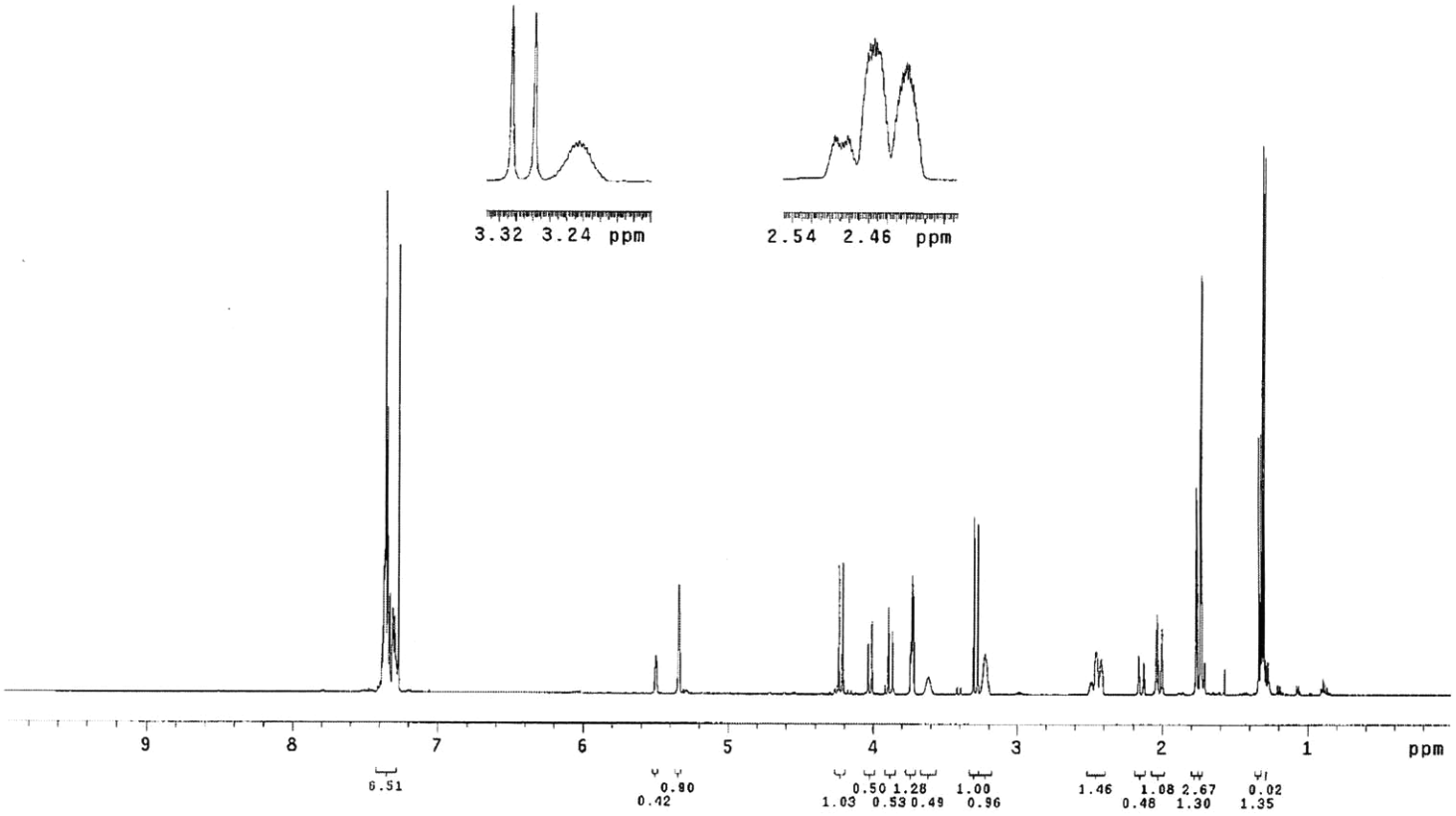


1-Benzyl-2-cyano-4,6-dimethyl-1,2,3,6-tetrahydropyridine (166). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.100 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.212 g, 1.47 mmol, 1.0 equiv) in 4 mL of CH_2Cl_2. The solution was cooled at -78 °C and 2,4-dimethylhexadiene (0.96 mL of 70:30 mixture of isomers, 0.69 g, 5.9 mmol, 4.0 equiv) was added in one portion via syringe. Methanesulfonic acid (0.73 M in CH_2Cl_2, 3.00 mL, 0.212 g, 2.20 mmol, 1.5 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -70 °C. The reaction mixture was stirred at -78 °C for 1.5 h and then added in one portion to 15 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 20 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.257 g of a yellow oil. Purification by column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.257 g (77%) of **166** (33:67 mixture of 2,6-*cis*: 2,6-*trans* substituted cycloadducts) as a colorless oil: IR (thin film) 3064, 3029, 2972, 2917, 1495, 1454, 1382, 1345, and 1330 cm^{-1}; For 2,6-*cis* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5 H), 5.50 (m, 1 H), 4.00 (AB q, J = 14.0 Hz, 2 H), 3.73 (dd, J = 6.5, 2.0 Hz, 1 H), 3.62 (m, 1 H), 2.46 (dm, J = 17.0 Hz, 1 H), 2.14 (d, J = 17.0 Hz, 1 H), 1.77 (s, 3 H), 1.33 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 129.0, 128.8, 127.8, 127.8, 126.2, 121.3, 56.2, 53.0, 44.2, 33.8, 23.1, 14.9; For 2,6-*trans* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5 H), 5.34 (d, J = 1.5 Hz, 1 H), 4.22 (d, J = 14.0 Hz, 1 H), 3.73 (dd, J = 5.8, 1.5 Hz, 1 H), 3.29 (d, J = 13.5 Hz, 1 H), 3.19-3.26 (m, 1 H), 2.44 (dm, J = 16.5 Hz, 1 H), 2.02 (d, J = 17.0 Hz, 1 H), 1.73 (s, 3 H), 1.31 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 129.1,

128.8, 128.5, 127.8, 126.2, 117.6, 55.8, 53.0, 48.2, 33.7, 22.8, 20.6; HRMS (m/z) $[M+H]^+$ calcd for $C_{15}H_{18}N_2$: 227.1543. Found: 227.1545.


CH3
Bn
N
H3C
CN

166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8
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5
4
3
2
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ppm
6.51
0.90
0.42
0.50 1.28
1.03 0.53 0.49
1.00
0.96
1.46
1.08 2.67
0.48 1.30
0.02
1.35

CH3
Bn
N
H3C
CN

166

129.064
128.977
128.817
128.757
128.542
127.814
127.796
127.769
126.249
126.180
137.822
137.574
121.296
117.597
77.486
77.230
76.978
56.158
55.883
53.078
52.981
48.246
44.151
33.755
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80
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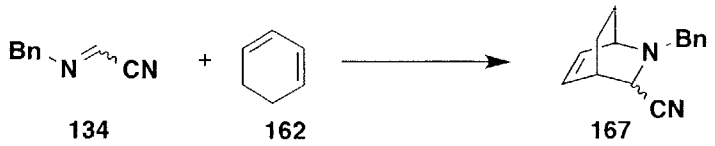
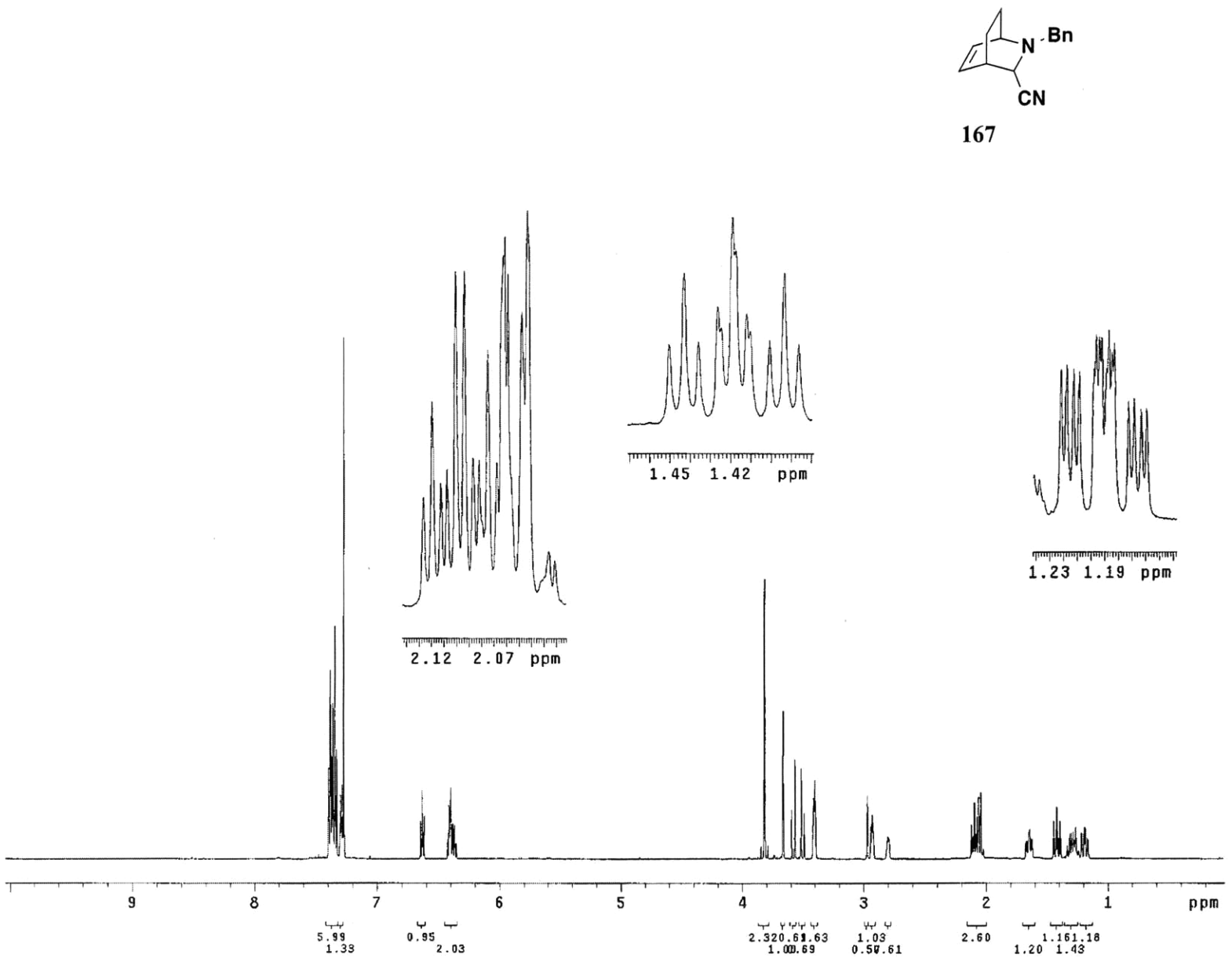
20
0 ppm



134 162 167

2-Aza-2-benzyl-3-cyano[2.2.2]bicyclooct-5-ene (167). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.060 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.200 g, 1.39 mmol, 1.0 equiv) in 6 mL of CH_2Cl_2. The solution was cooled at -78 °C and 1,3-cyclohexadiene (0.199 mL, 0.167 g, 1.39 mmol, 1.5 equiv) was added in one portion via syringe. Methanesulfonic acid (0.73 M in CH_2Cl_2, 1.90 mL, 0.134 g, 1.39 mmol, 1.0 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -75 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 20 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.210 g of a yellow oil. Purification by column chromatography on 15 g of Et_3N-deactivated silica gel (elution with 3% EtOAc-hexanes containing 1% Et_3N) afforded 0.128 g (41%) of **167** (64:36 mixture of endo:exo diastereomers) as a colorless oil: IR (thin film) 2930, 2856, 2361, 1692, 1462, 1199, and 839 cm^{-1}; For endo product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.40 (m, 5 H), 6.63 (ddd J = 8.5, 6.5, 1.5 Hz, 1 H), 6.40 (t, J = 7.0 Hz, 1 H), 3.82 (AB q, J = 14.5 Hz, 2 H), 3.66 (d, J = 2.5 Hz, 1 H), 3.41 (m, 1 H), 2.93 (m, 1 H), 2.10 (ddt, J = 12.5, 9.0, 3.5 Hz, 1 H), 1.65 (dddd, J = 13.0, 10.8, 4.5, 2.5 Hz, 1 H), 1.42 (ddt, J = 12.5, 12.0, 3.5 Hz, 1 H), 1.19 (dddd, J = 12.8, 11.8, 4.7, 2.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 136.7, 130.6, 129.0, 128.6, 127.7, 119.9, 58.6, 55.2, 50.3, 34.7, 22.7, 21.8; For exo product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.40 (m, 5 H), 6.35-6.43 (m, 2 H), 3.54 (AB q, J = 13.0 Hz, 2 H), 3.41 (m, 1 H), 2.97 (dd, J = 2.5, 2.0 Hz, 1 H), 2.80 (m, 1 H), 2.05 (m, 2 H), 1.30 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 133.5, 131.9, 129.2, 128.6, 127.7, 120.6, 61.6, 55.8, 50.8, 34.1, 26.7, 18.4; HRMS $(M+H)^+$ calc for $C_{15}H_{16}N_2$: 225.1386. Found: 225.1395.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1.23 1.19 ppm
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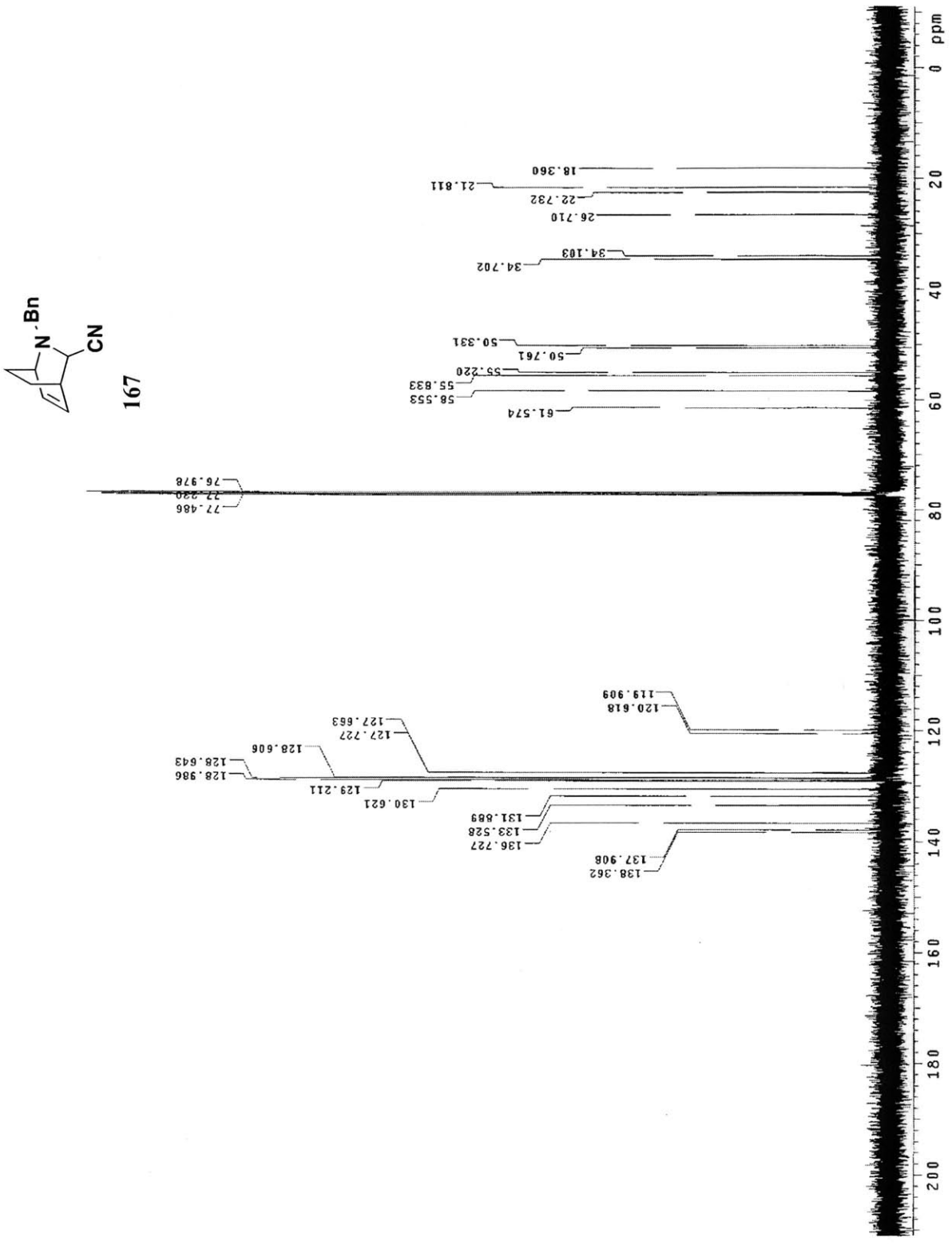
8
7
6
5
4
3
2
1
ppm
5.99
1.33
0.95
2.03
2.32
0.61
1.63
1.00
0.69
1.03
0.57
0.61
2.60
1.16
1.18
1.20
1.43

167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CN
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22.732
26.710
34.103
34.702
50.331
50.761
55.220
55.833
58.553
61.574
76.978
77.230
77.486
119.909
120.618
127.663
127.727
128.606
128.643
128.986
129.211
130.621
131.689
133.528
136.727
137.908
138.362
0
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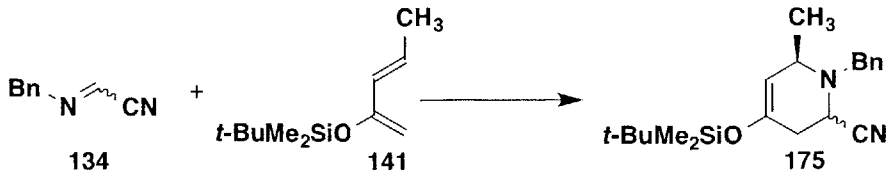
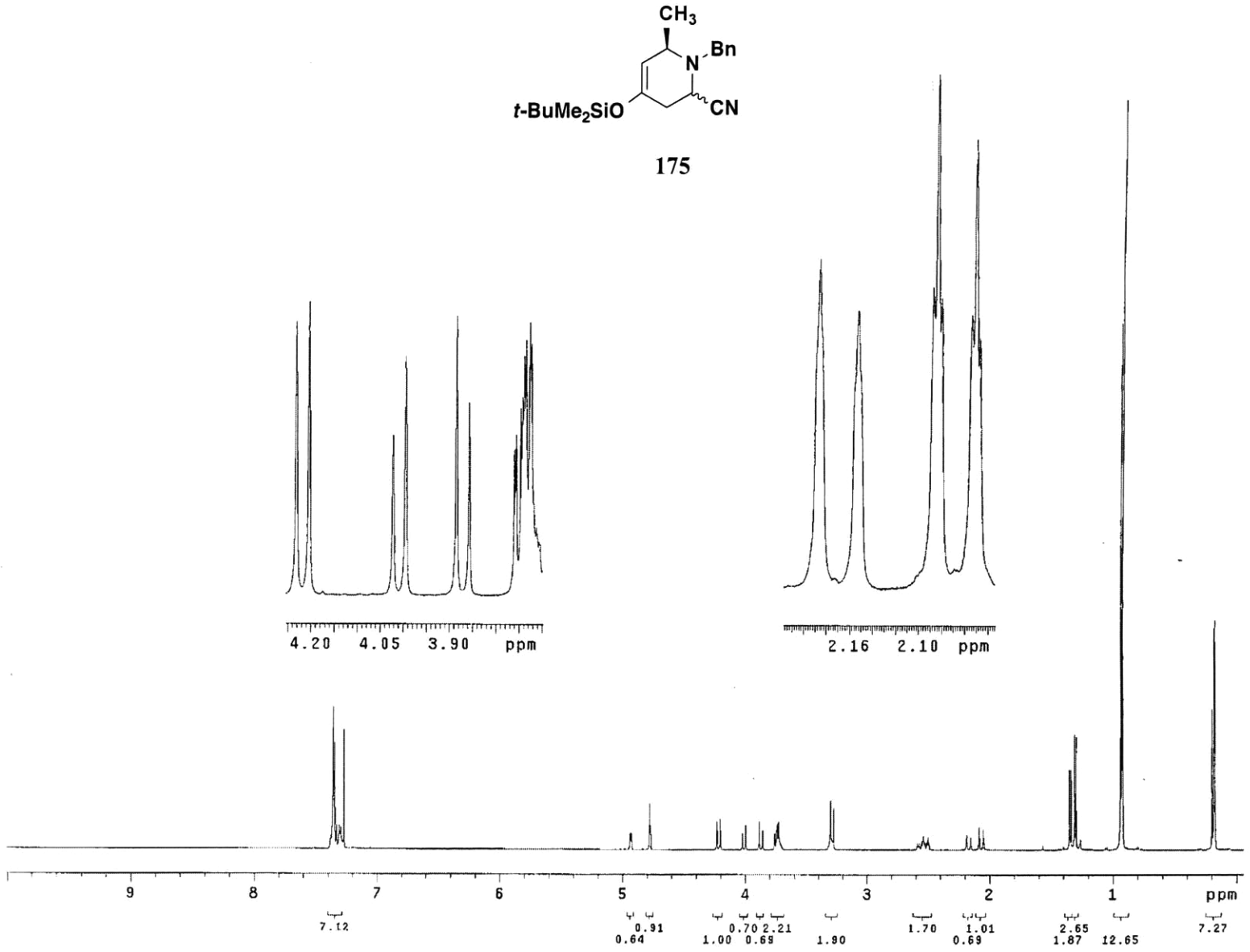
40
60
80
100
120
140
160
180
200
ppm



1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-cyano-6-methyl-1,2,3,6-tetrahydropyridine (175). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.100 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.100 g, 0.694 mmol, 1.0 equiv) in 2 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C and a solution of 2-(tert-butyldimethylsiloxy)-l,3-pentadiene (0.229 g of a 90:10 mixture of silyenol ethers, 1.04 mmol, 1.5 equiv) in 2 mL CH_2Cl_2 was added via cannula. Methanesulfonic acid (0.73 M in CH_2Cl_2, 0.95 mL, 0.066 g, 0.69 mmol, 1.0 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -72 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.241 g of a yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution hexanes containing 1% Et_3N) afforded 0.126 g (53%) of **175** (59:41 mixture of 2,6-*cis*: 2,6-*trans* substituted cycloadducts) as a colorless oil: IR (thin film) 3032, 2957, 2930, 2858, 1683, 1463, 1373, 1224, and 841 cm^{-1}; For 2,6-*cis* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5 H), 4.94 (dd, J = 4.0, 2.5 Hz, 1 H), 3.95 (AB q, J = 13.5 Hz, 2 H), 3.76 (dd, J = 7.0, 2.0 Hz, 1 H), 3.72 (m, 1 H), 2.57 (ddt, J = 19.0, 6.5, 2.5 Hz, 1 H), 2.18 (d, J = 17.0 Hz, 1 H), 1.36 (d, J = 7.0 Hz, 3 H), 0.95 (s, 9 H), 0.21 (s, 3 H), 0.20 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 137.6, 128.9, 128.8, 120.9, 108.6, 56.0, 52.8, 44.6, 33.5, 25.8, 15.9, -4.2, -4.3; For 2,6-*trans* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.32 (m, 5 H), 4.74 (t, J = 2.1 Hz, 1 H), 4.18 (d, J = 13.7 Hz, 1 H), 3.70 (dd, J = 5.7,

1.8 Hz, 1 H), 3.25 (d, J = 13.7 Hz, 1 H), 3.24-3.30 (m, 1 H), 2.48 (dm, J = 16.7 Hz, 1 H), 2.03 (dt, J = 16.7, 1.8 Hz, 1 H), 1.27 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 137.8, 129.0, 128.8, 127.9, 117.2, 108.6, 55.5, 52.3, 48.7, 33.7, 25.8, 21.4, 18.2, -4.3, -4.2; HRMS (m/z) $[M+H]^+$ calcd for $C_{20}H_{30}N_2OSi$: 343.2200. Found: 343.2205.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N
CN
t-BuMe2SiO
175
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2.16 2.10 ppm
9 8 7 6 5 4 3 2 1 ppm
7.12
0.64 0.91
1.00 0.69 0.70 2.21
1.90
1.70
0.69 1.01
1.87 2.65 12.65
7.27

CH3
Bn
N
t-BuMe2SiO
CN
175
145.668
144.972
137.831
137.565
129.005
128.886
128.840
128.785
127.847
120.911
117.176
108.652
108.569
77.482
77.230
76.974
55.989
55.495
52.794
52.322
48.651
44.563
33.650
33.494
25.803
25.789
21.386
18.163
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120
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80
60
40
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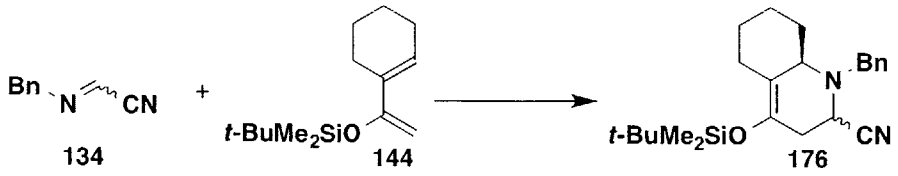
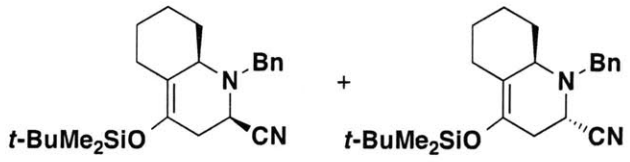
0
ppm



1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-cyano-1,2,3,5,6,7,8,8a-octahydroquinoline (176). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.060 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.103 g, 0.714 mmol, 1.0 equiv) in 2 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C and a solution of *tert*-butyl(1-cyclohexenylvinyloxy)dimethylsilane (0.254 g, 1.07 mmol, 1.5 equiv) in 2 mL CH_2Cl_2 was added via cannula. Methanesulfonic acid (0.73 M in CH_2Cl_2, 0.99 mL, 0.068 g, 0.71 mmol, 1.0 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -70 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 25 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.362 g of a yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution hexanes containing 1% Et_3N) afforded 0.156 g (57%) of **176** (64:36 mixture of 2,6-*cis*:2,6-*trans* substituted cycloadducts) as a colorless oil: IR (thin film) 2930, 2856, 2361, 1692, 1462, 1199, and 839 cm^{-1}; For 2,6-*cis* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5 H), 4.03 (d, J = 13.5 Hz, 1 H), 3.86 (d, J = 14.0 Hz, 1 H), 3.71 (dd, J = 6.5, 2.0 Hz, 1 H), 3.37 (d, J = 11.5 Hz, 1 H), 2.95 (m, 1 H), 2.60 (dm, J = 15.5 Hz, 1 H), 2.20 (d, J = 17.0 Hz, 1 H), 2.08 (m, 1 H), 1.97 (dq, J = 12.0, 3.6 Hz, 1 H), 1.83-1.90 (m, 1 H), 1.70-1.77 (m, 1 H), 1.49-1.60 (m, 1 H), 1.20-1.34 (m, 2 H), 0.95 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 136.1, 128.9, 128.8, 127.8, 121.1, 118.3, 60.5, 55.5, 45.3, 34.0, 27.9, 27.1, 26.8, 26.1, 25.9, 18.3, -3.6, -3.7; For 2,6-*trans* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.28 (m, 5 H), 4.24 (d, J = 13.5 Hz, 1 H), 3.69 (m, 1 H), 3.31 (d, J = 13.5 Hz, 1 H),

2.91-3.00 (m, 2 H), 2.53 (dm, J = 16.5 Hz, 1 H), 2.36 (m, 1 H), 2.10 (d, J =16.0 Hz, 1 H), 1.85 (d, J = 13.5 Hz, 1 H), 1.76 (d, J = 12.5 Hz, 1 H), 1.57 (t, J = 13.5 Hz), 1.42 (qt, J = 13.5, 3.5 Hz, 1 H), 1.23 (m, 2 H), 0.95 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.1, 129.0, 128.8, 127.8, 117.5, 117.4, 59.4, 55.6, 48.1, 33.7, 33.5, 26.5, 25.9, 25.5, 25.0, 18.3, -3.7; HRMS (m/z) [M-H] calcd for $C_{23}H_{34}N_2OSi$: 381.2357. Found: 281.2351.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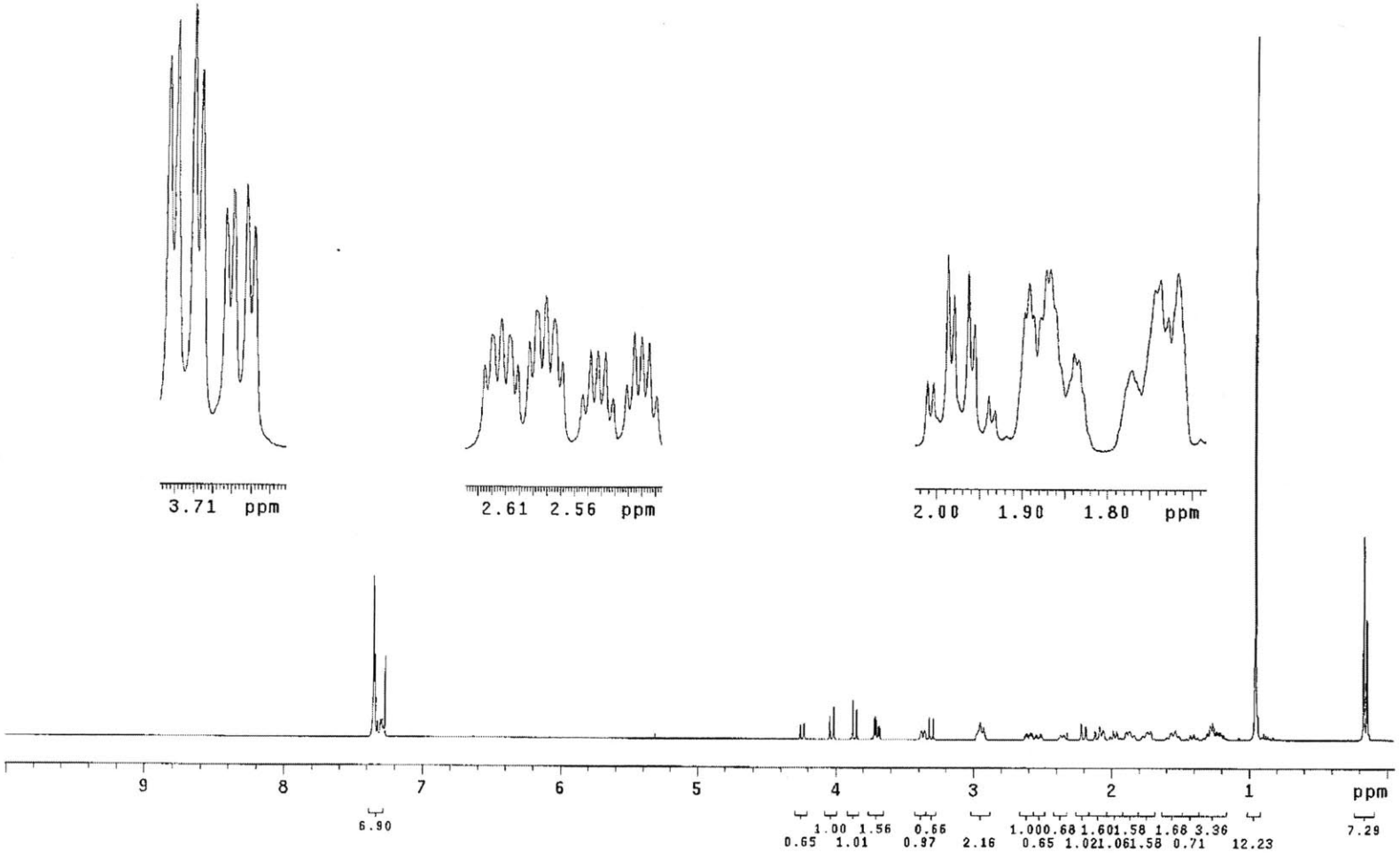
N
CN
t-BuMe2SiO
+
Bn
N
CN
t-BuMe2SiO

176a **176b**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7
6
5
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3
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1
ppm
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2.16
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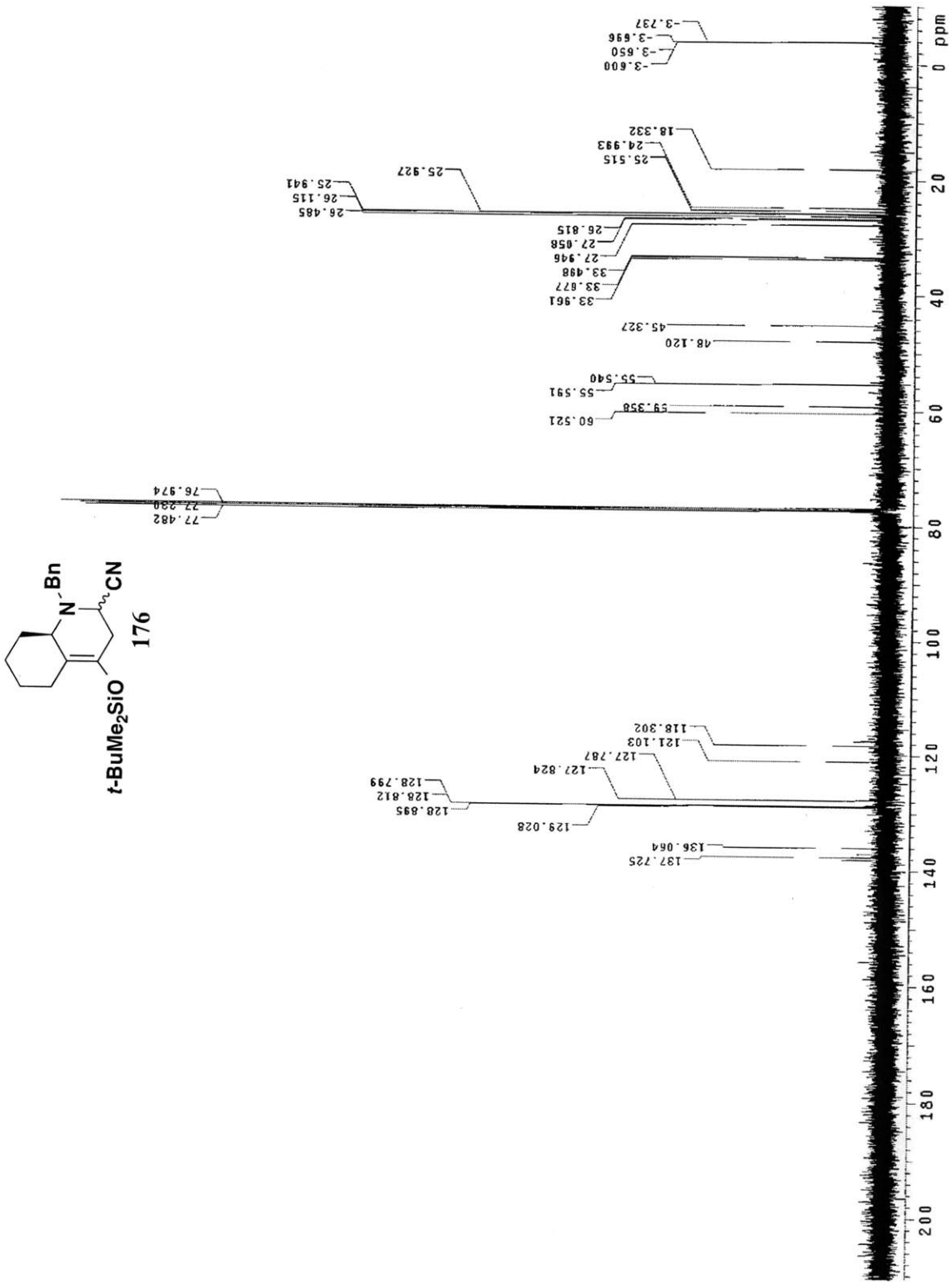
12.23
7.29


Bn
N
CN
t-BuMe2SiO
176
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-3.600
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25.927
25.941
26.115
26.485
26.815
27.058
27.946
33.488
33.877
33.961
45.327
48.120
55.540
55.591
59.358
60.521
76.974
77.220
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128.895
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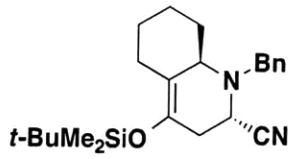
137.725
ppm


Bn
N
t-BuMe2SiO
CN

176a

9
8
7
6
5
4
3
2
1
ppm
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1.02
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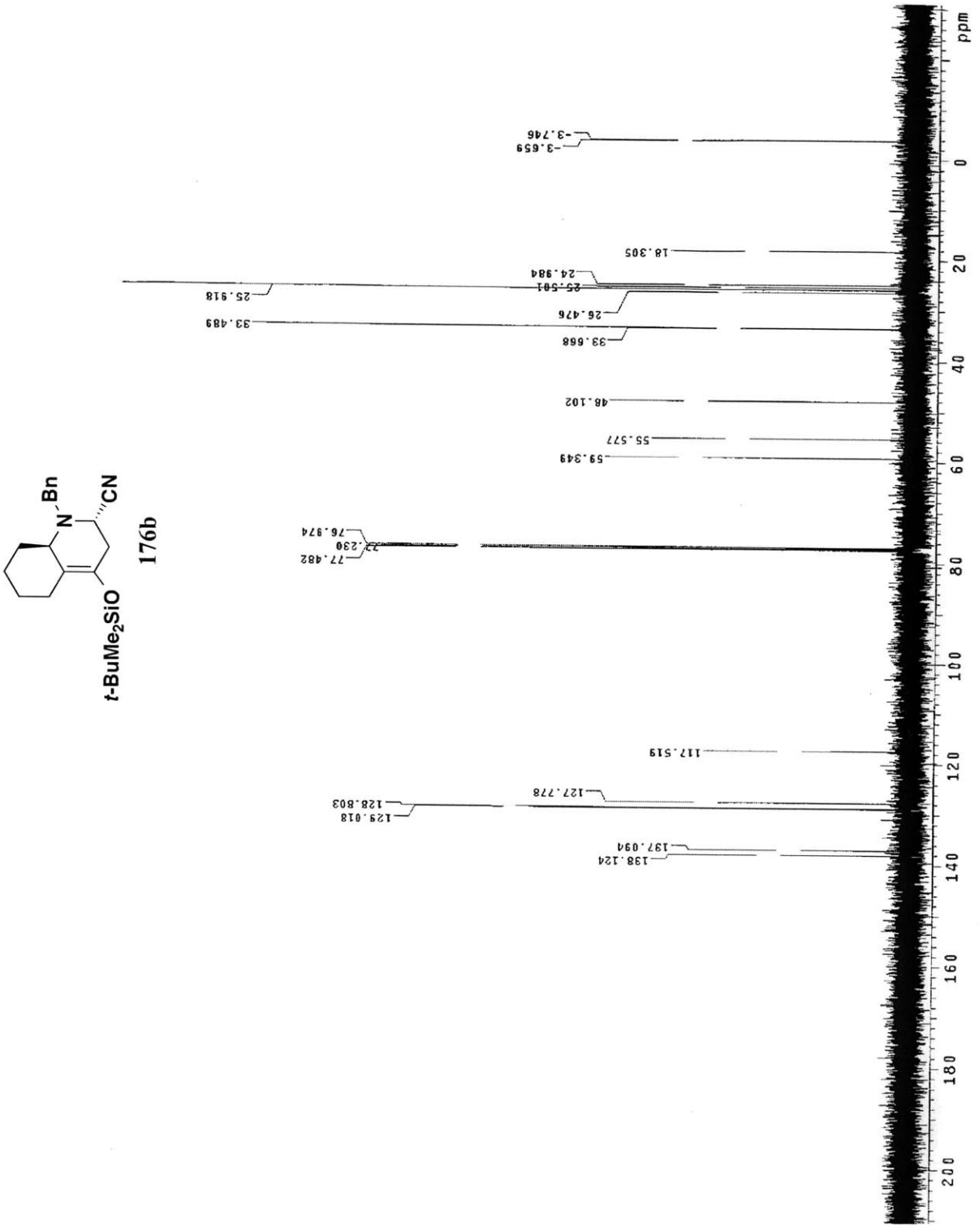
4.67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33.489
33.668
48.102
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59.349
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77.230
77.482
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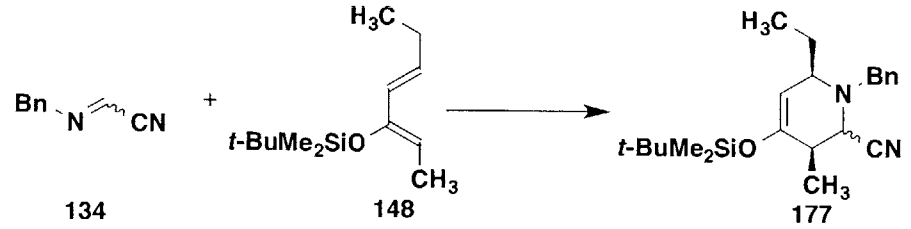
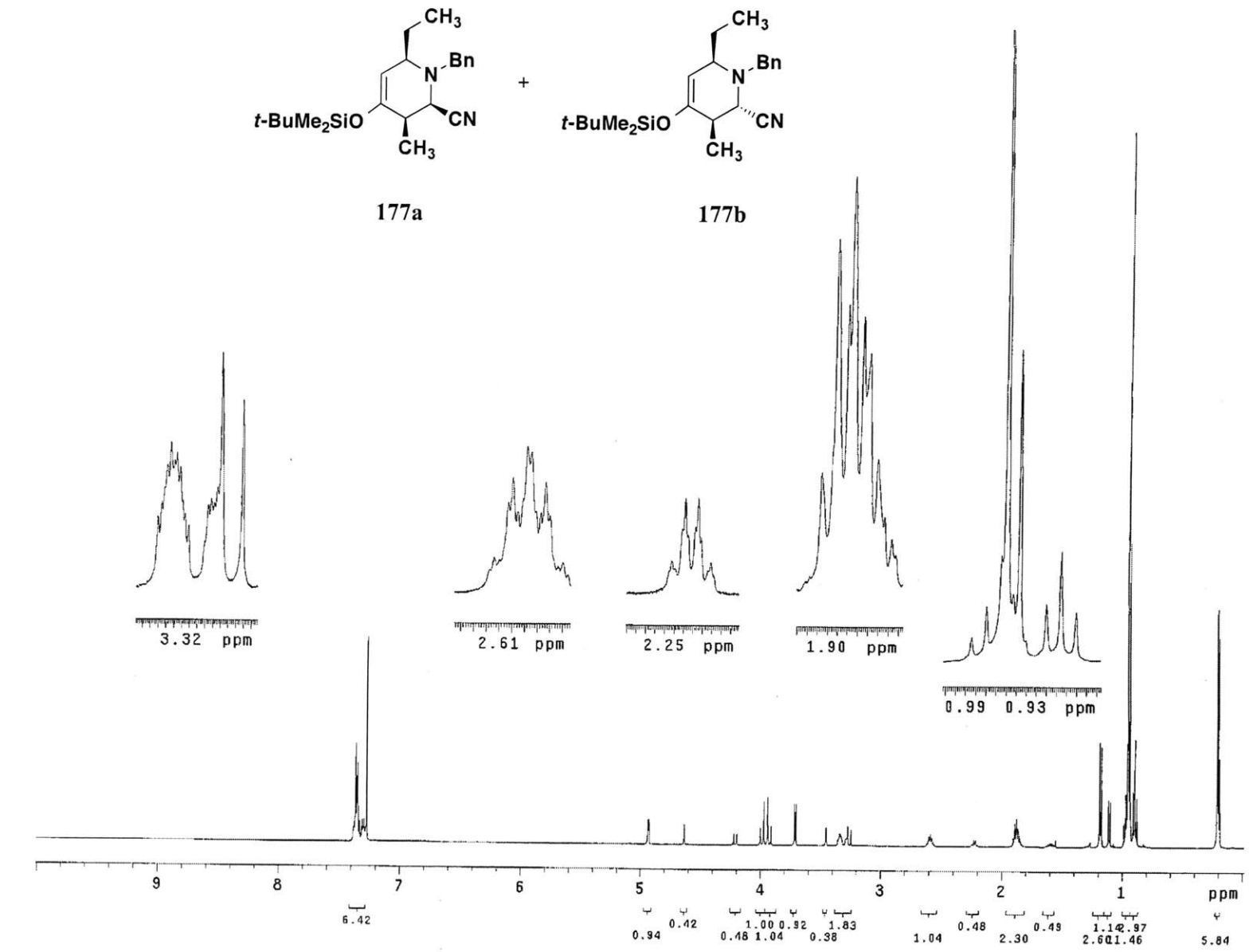
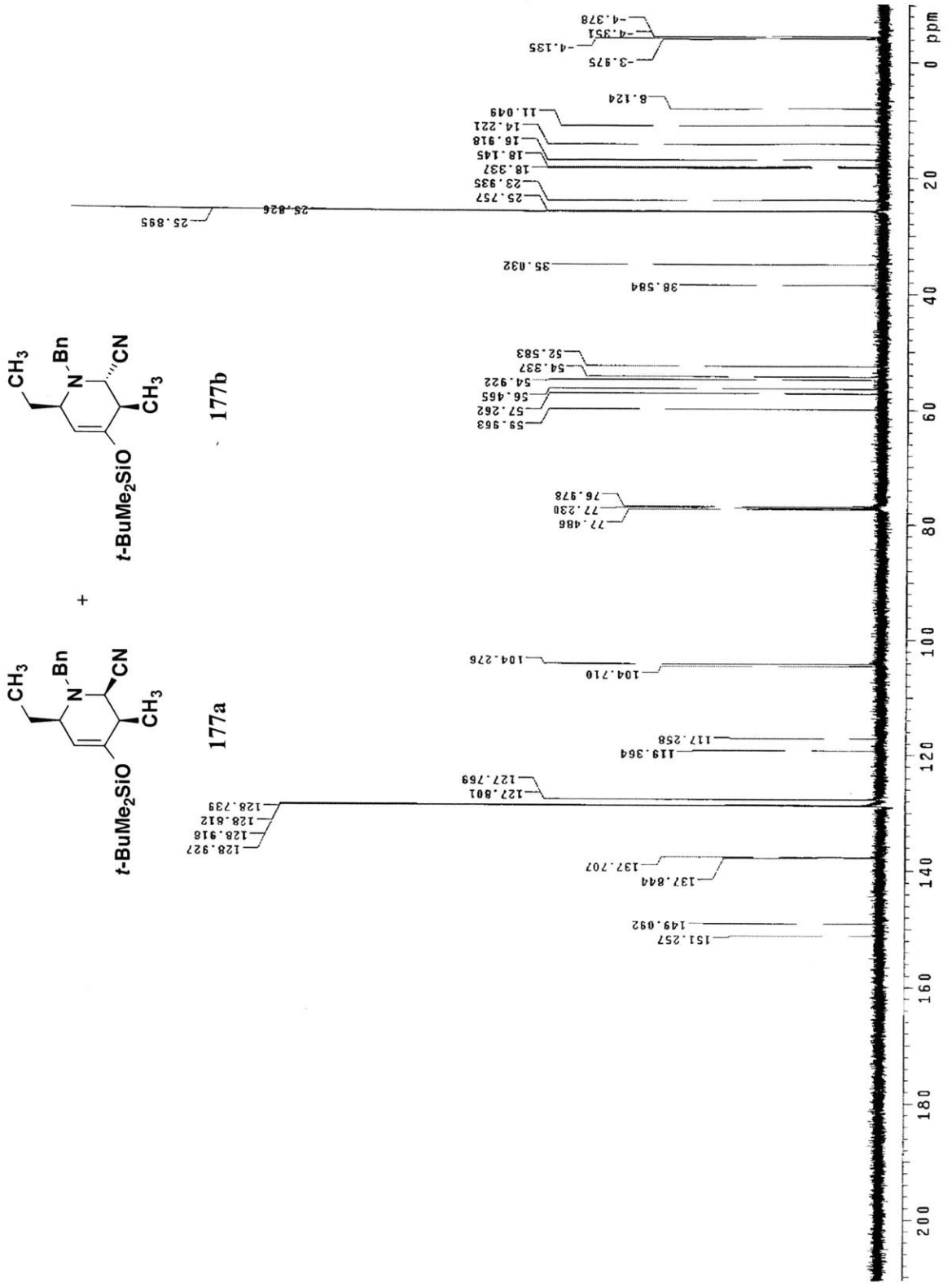
200

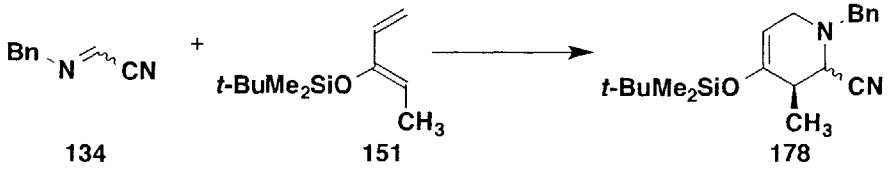


1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-cyano-6-ethyl-3-methyl-1,2,3,6-tetrahydropyridine (177). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.030 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.098 g, 0.68 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C and a solution of (2Z,4E)-3-(*tert*-butyldimethylsiloxy)-2,4-heptadiene (0.310 g of a 75:25 mixture of sily enol ethers, 1.03 mmol, 1.5 equiv) in 1 mL CH_2Cl_2 was added via cannula. Methanesulfonic acid (0.73 M in CH_2Cl_2, 0.93 mL, 0.089 g, 0.68 mmol, 1.0 equiv) was then added dropwise over 1 min at a rate such that the internal temperature did not rise above -75 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 15 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 20 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.261 g of a yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.206 g (82%) of **177** (70:30 mixture of 2,6-*cis*:2,6-*trans* substituted cycloadducts) as a colorless oil: IR (thin film) 2964, 2913, 2858, 2225, 1677, 1463, 1362, 1297, and 876 cm^{-1}; For 2,6-*cis* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5 H), 4.93 (dd, J = 4.0, 1.5 Hz, 1 H), 3.96 (AB q, J = 14.0 Hz, 2 H), 3.71 (d, J = 6.0 Hz, 1 H), 3.31-3.35 (m, 1 H), 2.55-2.61 (m, 1 H), 1.83-1.91 (m, 2 H), 1.18 (d, J = 7.0 Hz, 3 H), 0.95 (s, 9 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.21 (s, 3 H), and 0.20 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 137.7, 128.9, 128.7, 119.4, 104.3, 60.0, 56.4, 52.6, 35.0, 25.9, 23.9, 18.3, 14.2, 11.1, -4.1, -4.3; For 2,6-*trans* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5 H), 4.63 (d, J = 2.5 Hz, 1 H), 4.21 (d, J = 14.0 Hz, 1 H), 3.45 (d, J = 2.0 Hz, 1 H), 3.28 (m, 1 H), 3.26

(d, J = 14.0 Hz, 1 H), 2.22 (dt, J = 7.0, 1.5 Hz, 1 H), 1.87 (dqd, J = 14.5, 8.5, 6.0 Hz, 1 H), 1.59 (dm, J = 2.5 Hz, 1 H), 1.11 (d, J = 6.5 Hz, 3 Hz), 0.97 (t, J = 7.5 Hz, 3 H), 0.94 (s, 9 H), 0.21 (s, 3 H), 0.19 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 137.9, 128.9, 128.8, 127.8, 117.3, 104.7, 57.3, 54.9, 54.3, 38.6, 25.8, 25.8, 18.2, 16.9, 8.1, -4.0, -4.3; HRMS (m/z) $[M+H]^+$ calcd for $C_{22}H_{34}N_2OSi$: 371.2513. Found: 371.2516.


CH3
N
Bn
t-BuMe2SiO
CN
CH3
+
CH3
N
Bn
t-BuMe2SiO
CN
CH3
177a
177b
3.32 ppm
2.61 ppm
2.25 ppm
1.90 ppm
0.99 0.93 ppm
9
8
7
6
5
4
3
2
1
ppm
6.42
0.94
0.42
0.48
1.00
1.04
0.92
0.38
1.83
1.04
0.48
2.30
0.49
2.60
1.46
5.84

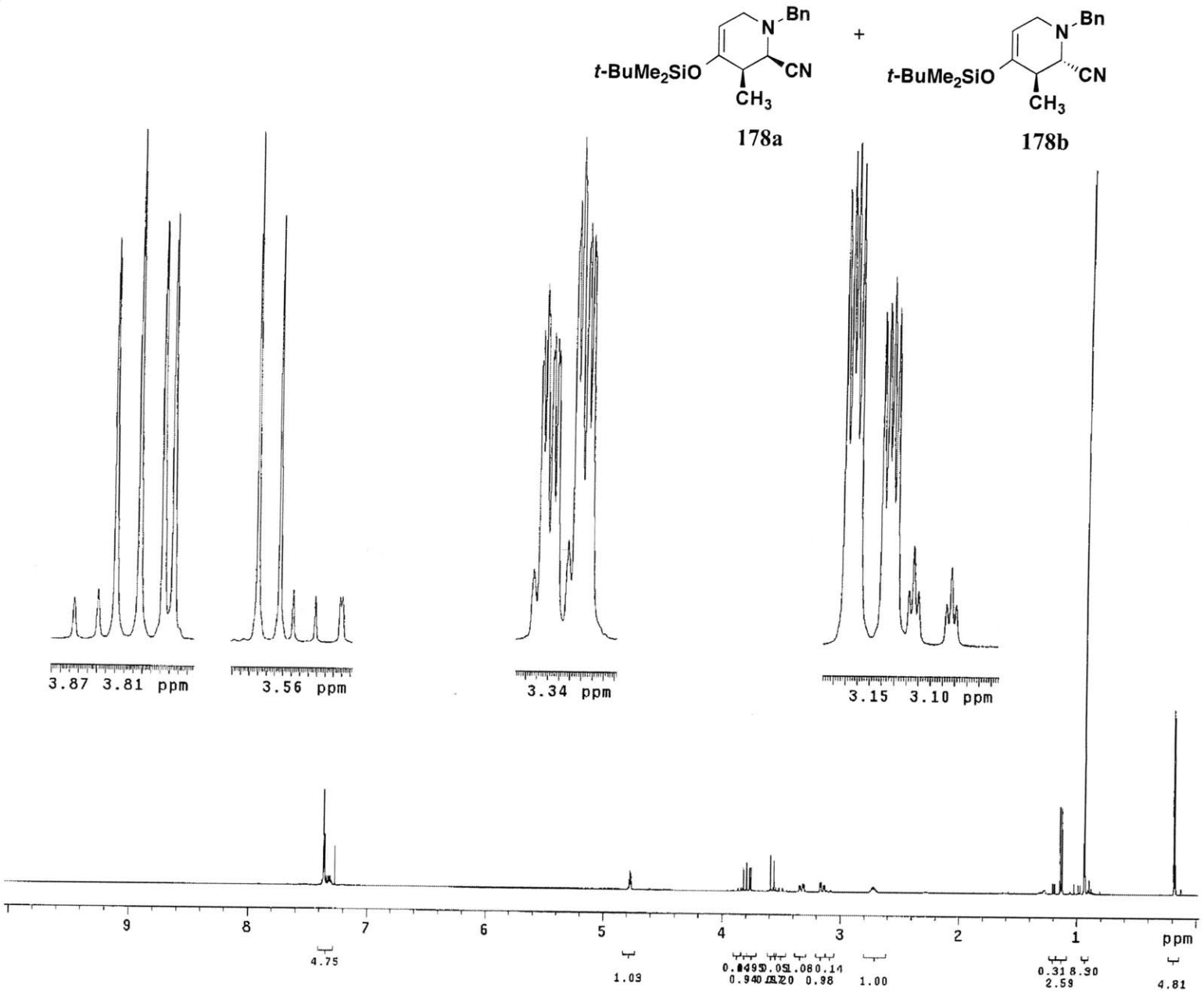

CH3
Bn
N
CN
CH3
t-BuMe2SiO
177b
+
177a
-4.378
-4.351
-4.135
-3.975
8.124
11.049
14.221
16.918
18.145
18.337
23.935
25.757
25.826
25.895
35.032
38.584
52.583
54.337
54.922
56.465
57.262
59.963
76.978
77.230
77.486
104.276
104.710
117.258
119.364
127.769
127.801
128.739
128.812
128.918
128.927
137.707
137.844
149.092
151.257
0 ppm
20
40
60
80
100
120
140
160
180
200

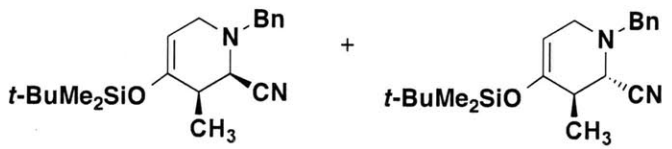


134 151 178

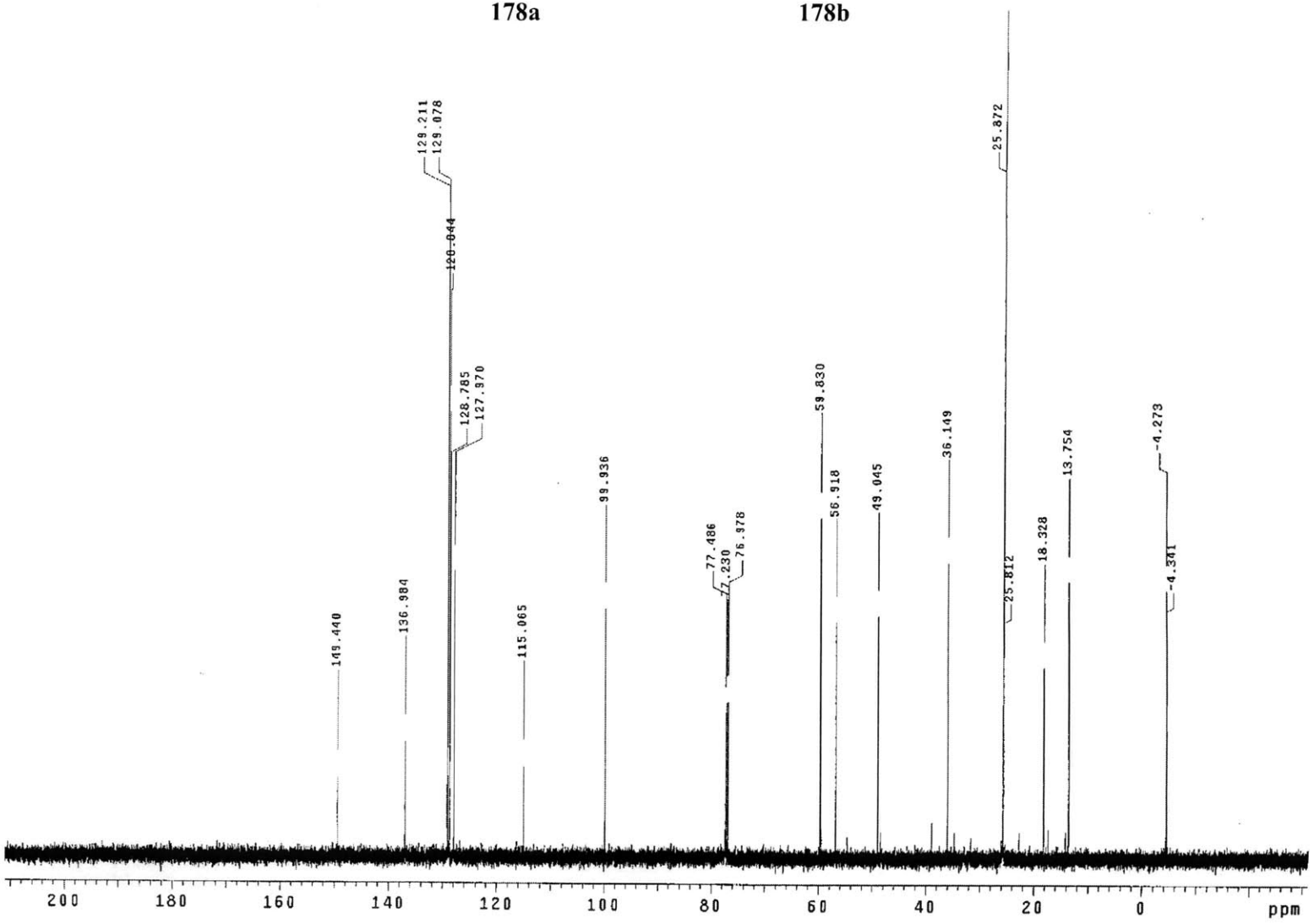
1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-cyano-3-methyl-1,2,3,6-tetrahydropyridine (178). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.040 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.100 g, 0.690 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C and a solution of 3-(tert-butyldimethylsiloxy)-1,3-pentadiene (0.206 g, 1.04 mmol, 1.5 equiv) in 1 mL CH_2Cl_2 was added via cannula. Methanesulfonic acid (0.73 M in CH_2Cl_2, 0.95 mL, 0.066 g, 0.69 mmol, 1.0 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -78 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 15 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 20 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.198 g of a yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.175 g (74%) of **178** (87:13 mixture of 2,6-*cis*:2,6-*trans* substituted cycloadducts) as a colorless oil: IR (thin film) 3030, 2931, 2858, 2220, 1674, 1463, 1359, 1169, 1116, and 867 cm^{-1}; For 2,6-*cis* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5 H), 4.77 (m, 1 H), 3.81 (d, J = 13.0 Hz, 1 H), 3.76 (d, J = 5.5 Hz, 1 H), 3.58 (d, J = 13.5 Hz, 1 H), 3.32 (ddd, J = 15.5, 4.8, 0.7 Hz, 1 H), 3.15 (ddd, J = 15.5, 3.7, 2.2 Hz, 1 H), 2.72 (m, 1 H), 1.13 (d, J = 7.5 Hz, 3 H), 0.93 (s, 9 H), 0.19 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 137.0, 129.2, 128.8, 128.0, 115.1, 99.9, 59.8, 56.9, 49.0, 36.2, 25.9, 18.3, 13.8, -4.3; For 2,6-*trans* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5 H), 4.77 (m, 1 H), 3.85 (d, J = 13.0 Hz, 1 H), 3.54 (d, J = 13.0 Hz, 1 H), 3.49 (d, J = 1.5 Hz, 1 H), 3.33 (m, 1 H), 3.10 (dt, J = 15.5, 1.9 Hz, 1 H), 2.28 (br q, J = 7.0 Hz, 1 H), 1.20 (d, J = 7.0 Hz, 3 H), 0.93

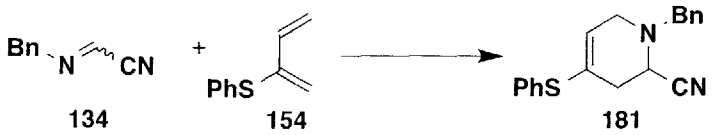
(s, 9 H), 0.19 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.4, 137.1, 129.1, 128.8, 127.9, 100.0, 59.6, 54.9, 48.5, 39.0, 25.8, 18.2, 17.5, -4.2, -4.3; HRMS (m/z) [M-H] calcd for $C_{20}H_{30}N_2OSi$: 341.2044. Found: 341.2056.


t-BuMe2SiO
N
Bn
CN
CH3
178a
+
t-BuMe2SiO
N
Bn
CN
CH3
178b
3.87 3.81 ppm
3.56 ppm
3.34 ppm
3.15 3.10 ppm
9
8
7
6
5
4
3
2
1
ppm
4.75
1.03
1.00
2.59
4.81

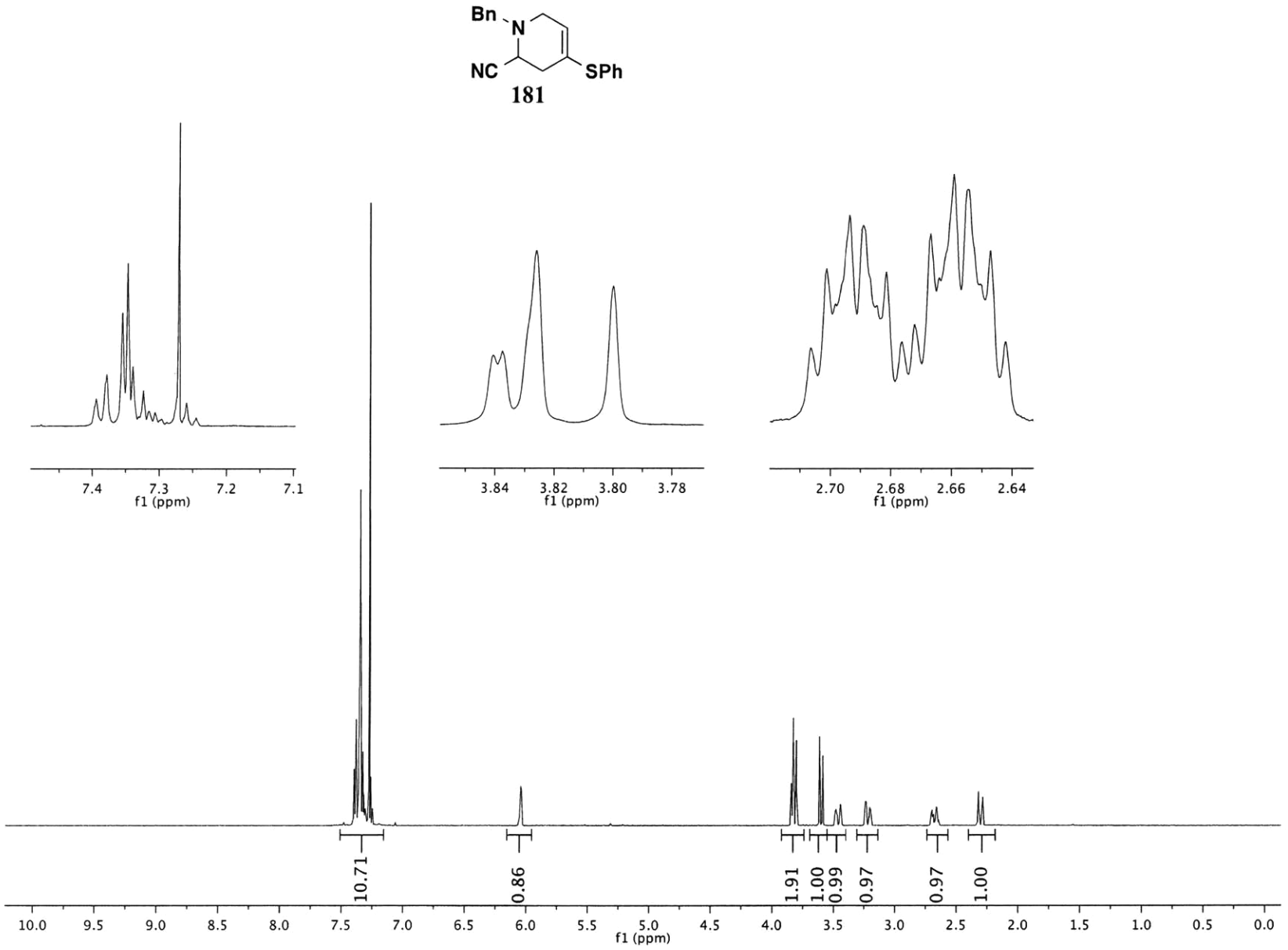

Bn
N
t-BuMe2SiO
CN
CH3
+
Bn
N
t-BuMe2SiO
CN
CH3

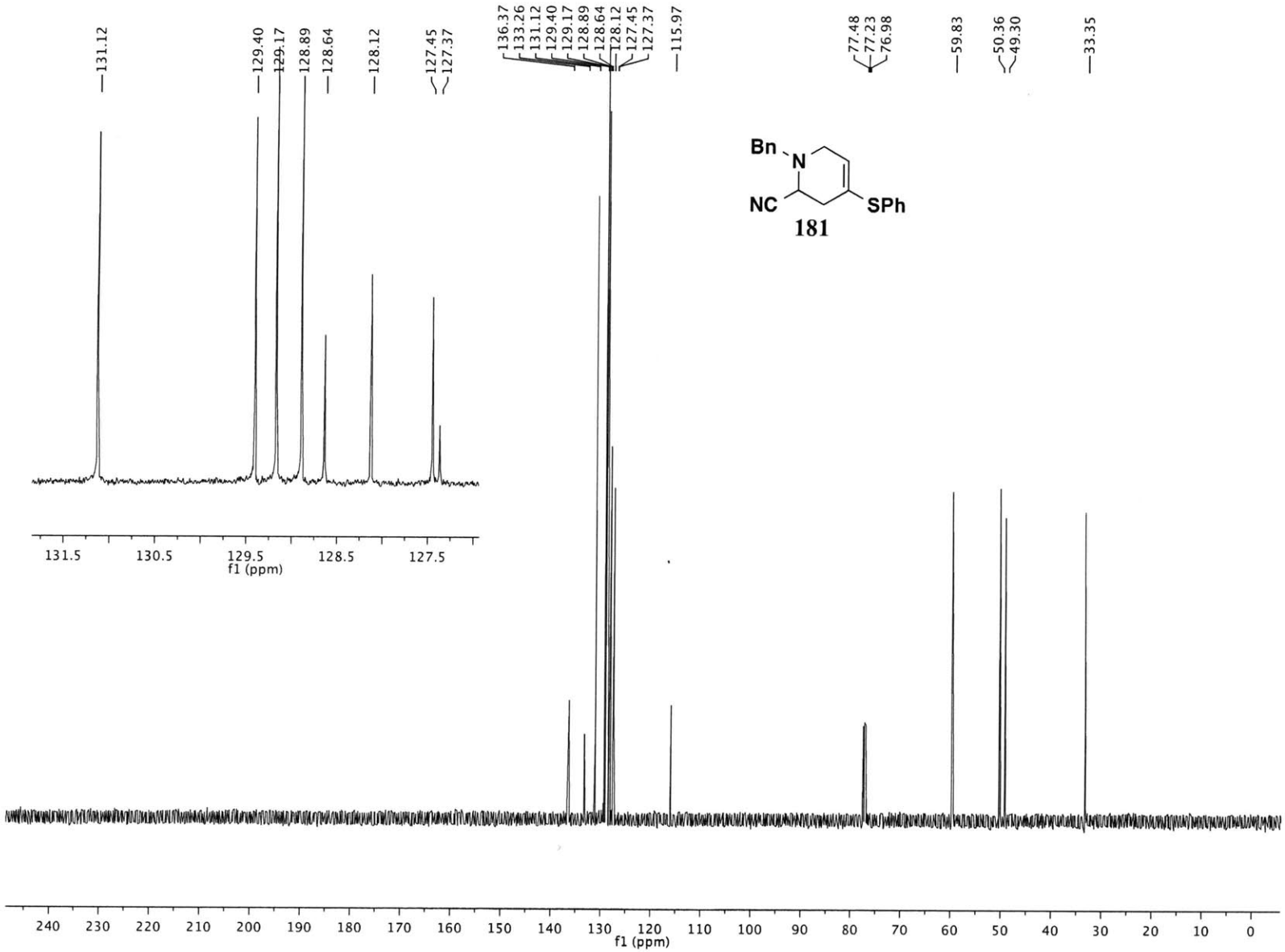
178a **178b**

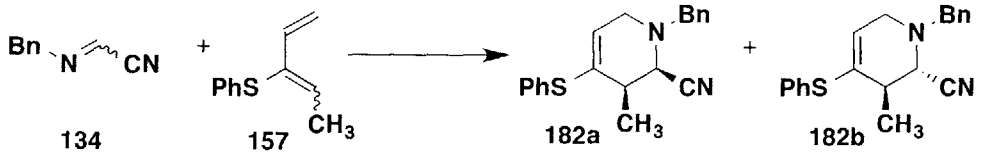

129.211
129.078
120.044
128.785
127.970
115.065
99.936
77.486
77.230
76.978
59.830
56.918
49.045
36.149
25.872
25.812
18.328
13.754
-4.273
-4.341
149.440
136.984
200
180
160
140
120
100
80
60
40
20
0
ppm



1-Benzyl-4-(phenylthio)-2-cyano-1,2,3,6-tetrahydropyridine (181). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.030 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.173 g, 1.20 mmol, 1.0 equiv) in 4 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C and a solution of 2-(phenylthio)-butadiene (0.292 g, 1.80 mmol, 1.5 equiv) in 1.5 mL CH_2Cl_2 was added via cannula. Methanesulfonic acid (0.73 M in CH_2Cl_2, 1.64 mL, 0.115 g, 1.20 mmol, 1.0 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -74 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 15 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 15 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.325 g of an orange oil. Purification by column chromatography on 20 g of Et_3N-deactivated silica gel (elution with 10% hexanes-benzene containing 1% Et_3N) afforded 0.292 g (79%) of **181** as a colorless oil: IR (thin film) 3061, 2921, 2818, 2223, 1582, 1475, 1354, 738, and 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.40 (m, 10 H), 6.05 (m, 1 H), 3.84 (dd, J = 6.0, 1.5 Hz, 1 H), 3.81 (d, J = 13.0 Hz, 1 H), 3.60 (d, J = 13.0 Hz, 1 H), 3.46 (dm, J = 17.5 Hz, 1 H), 3.22 (dm, J = 17.5 Hz, 1 H), 2.68 (dm, J = 18.0 Hz, 1 H), 3.36 (d, J = 17.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 133.3, 131.1, 129.4, 129.2, 128.9, 128.6, 128.1, 127.45, 127.37, 116.0, 59.8, 50.4, 49.3, 33.3; HRMS (m/z) [M-H] calcd for $C_{19}H_{18}N_2S$: 305.1107. Found: 305.1111.

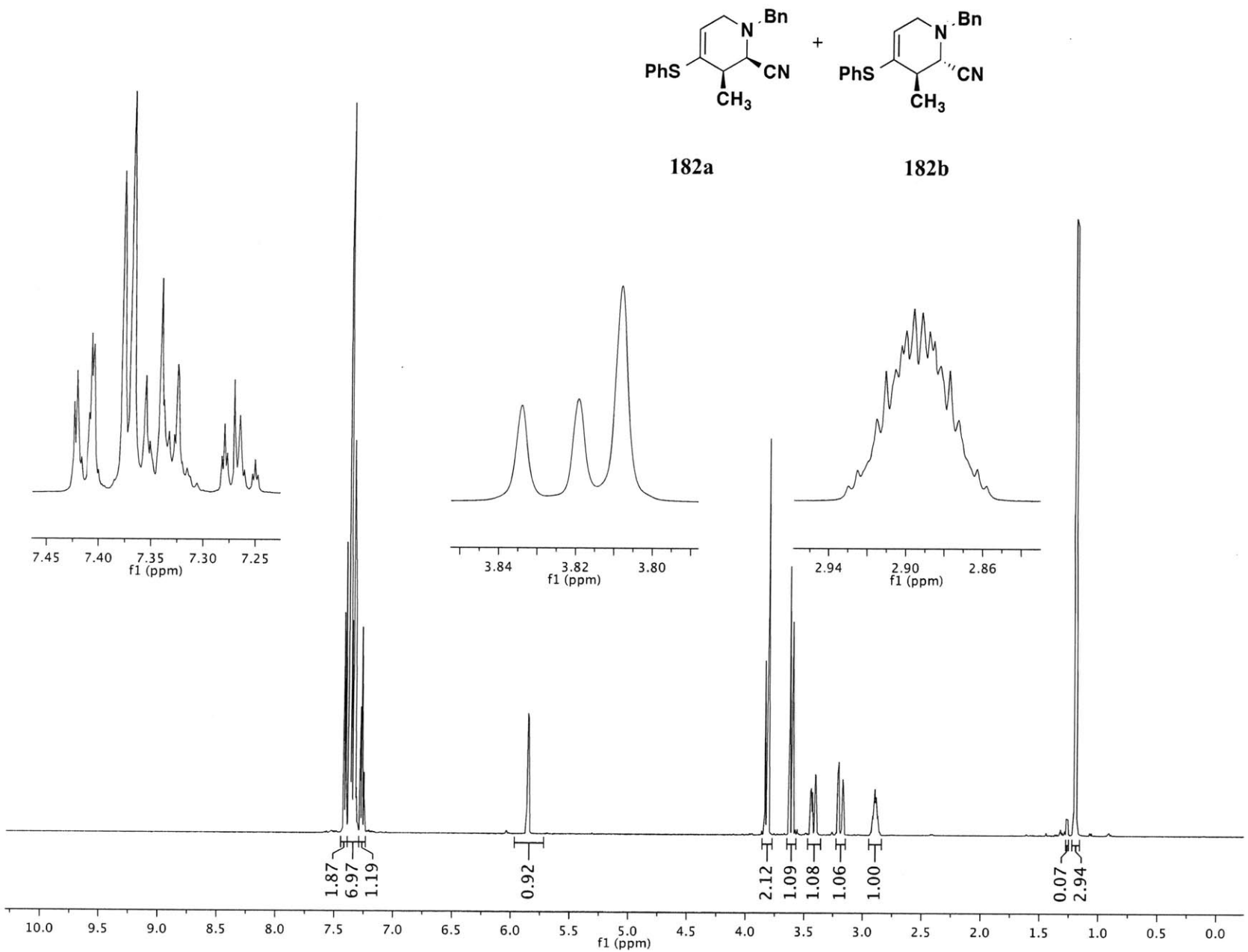

Bn
N
NC
SPh
181
7.4
7.3
7.2
7.1
f1 (ppm)
3.84
3.82
3.80
3.78
f1 (ppm)
2.70
2.68
2.66
2.64
f1 (ppm)
10.71
0.86
1.91
1.00
0.99
0.97
0.97
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

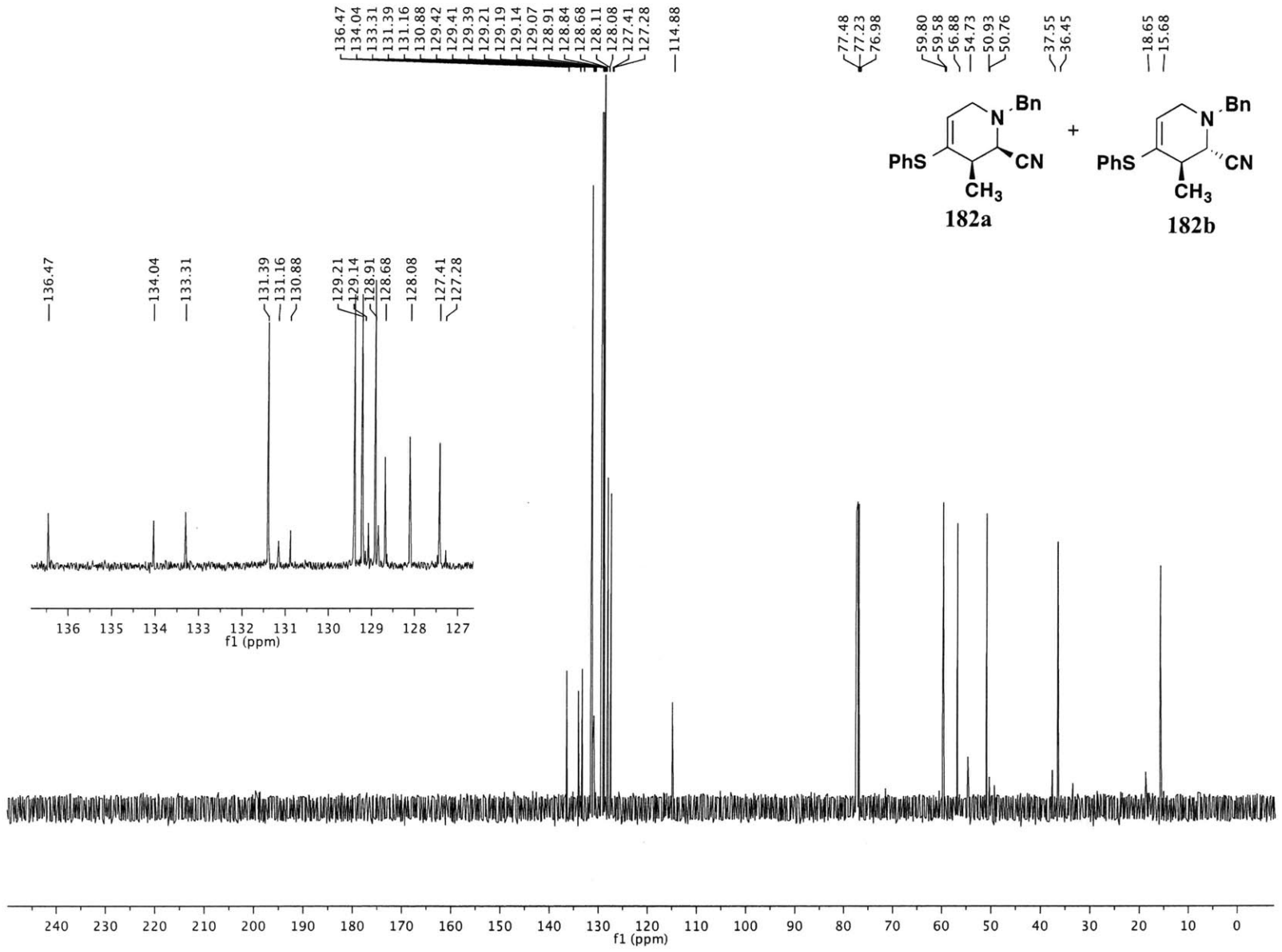

131.12
129.40
129.17
128.89
128.64
128.12
127.45
127.37
136.37
133.26
131.12
129.40
129.17
128.89
128.64
128.12
127.45
127.37
115.97
77.48
77.23
76.98
59.83
50.36
49.30
33.35
Bn
N
NC
SPh
181
131.5
130.5
129.5
128.5
127.5
f1 (ppm)
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

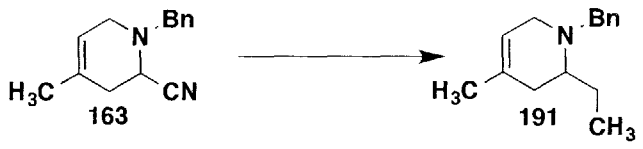


1-Benzyl-2-cyano-3-methyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine (182). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with 0.066 g of powdered 4 Å molecular sieves and a solution of imine **134** (0.069 g, 0.48 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C and a solution of 3-(phenylthio)-1,3-pentadiene (0.176 g of a 72:28 *E/Z* mixture, 0.72 mmol, 1.5 equiv) in 2 mL CH_2Cl_2 was added via cannula. Methanesulfonic acid (0.73 M in CH_2Cl_2, 0.66 mL, 0.046 g, 0.48 mmol, 1.0 equiv) was then added dropwise over 2 min at a rate such that the internal temperature did not rise above -73 °C. The reaction mixture was stirred at -78 °C for 2 h and then added in one portion to 10 mL of satd $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 15 mL of a satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.199 g of an orange oil. Purification by column chromatography on 15 g of Et_3N-deactivated silica gel (elution with 3% EtOAc-hexanes containing 1% Et_3N) afforded 0.106 g (69%) of a 98:2 mixture of **182a** and **182b** as a colorless oil: For **182a**: IR (thin film) 3061, 2930, 2876, 2820, 2223, 1582, 1455, 1337, 1084, 1024, 745, and 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.45 (m, 10 H), 5.85 (ddd, *J* = 4.9, 2.5, 2.0 Hz, 1 H), 3.82 (d, *J* = 13.0 Hz, 1 H), 3.81 (d, *J* = 6.0 Hz, 1 H), 3.61 (d, *J* = 13.0 Hz, 1 H), 3.42 (m, 1 H), 3.19 (ddd, *J* = 17.5, 4.0, 2.2 Hz, 1 H), 2.89 (m, 1 H), 1.20 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 134.0, 133.3, 131.3, 129.4, 129.2, 128.9, 128.7, 128.1, 127.4, 114.9, 59.8, 56.9, 50.9, 36.4, 15.7; For **182b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.40 (m, 10 H), 6.03 (dd, *J* = 4.6, 2.5 Hz, 1 H), 3.84 (d, *J* = 13.0 Hz, 1 H), 3.58 (d, *J* = 13.0 Hz,) 3.55 (d, *J* = 1.5 Hz, 1 H), 3.46 (dd, *J* = 17.5, 4.0 Hz, 1 H), 3.24 (dt, *J* = 17.5, 2.3 Hz, 1 H), 2.41 (br q, *J* = 6.5 Hz, 1 H), 1.25 (d, *J* = 6.5 Hz, 3 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 136.6, 133.8, 133.2, 130.9, 129.4, 129.2, 129.1, 128.9, 128.1, 127.3, 116.0, 59.6, 54.7, 50.8, 37.6, 18.7; HRMS (m/z) $[M+H]^+$ calcd for $C_{20}H_{20}N_2S$: 321.1420. Found: 321.1426.


Bn
N
PhS
CN
CH3
+
182a
182b
7.45 7.40 7.35 7.30 7.25
f1 (ppm)
3.84 3.82 3.80
f1 (ppm)
2.94 2.90 2.86
f1 (ppm)
1.87
6.97
1.19
0.92
2.12
1.09
1.08
1.06
1.00
0.07
2.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


136.47
134.04
133.31
131.39
131.16
130.88
129.42
129.41
129.39
129.21
129.19
129.14
129.07
128.91
128.84
128.68
128.11
128.08
127.41
127.28
114.88
77.48
77.23
76.98
59.80
59.58
56.88
54.73
50.93
50.76
37.55
36.45
18.65
15.68
PhS
Bn
N
CN
CH3
182a
182b
f1 (ppm)

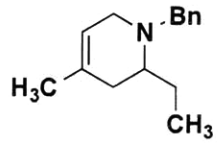


1-Benzyl-2-ethyl-4-methyl-1,2,3,6-tetrahydropyridine (191). A 25-mL, two necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **163** (0.098 g, 0.47 mmol, 1.0 equiv) in 3 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.65 M in Et_2O, 0.35 mL, 0.13 g, 0.94 mmol, 2.0 equiv) was added dropwise via syringe over 2 min. The reaction mixture was allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.091 g of an orange oil. Purification by column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) afforded 0.077 g (76%) of **191** as a light yellow oil: IR (thin film) 3026, 2961, 2928, 1602, 1494, 1453, 1377, 1159, 1093, 1073, and 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2 H), 7.31 (m, 2 H), 7.24 (m, 1 H) 5.30 (m, 1 H), 3.72 (d, J = 13.0 Hz, 1 H), 3.52 (d, J = 13.0 Hz, 2 H), 3.04 (dm, J = 17.0 Hz, 1 H), 2.93 (dm, J = 17.0 Hz, 1 H), 2.67 (qd, J = 8.3, 5.5 Hz, 1 H), 2.12 (d, J = 17.0 Hz, 1 H), 1.86 (d, J = 17.5, 1 H), 1.69 (s, 3 H), 1.72-1.63 (m, 1 H), 1.49-1.38 (m, 1 H), 0.95 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 131.9, 129.2, 128.4, 126.9, 118.8, 58.1, 56.3, 49.1, 32.9, 23.6, 22.4, 11.1; HRMS (m/z) $[M+H]^+$ calcd for $C_{15}H_{21}N$: 216.1747 Found: 216.1747.

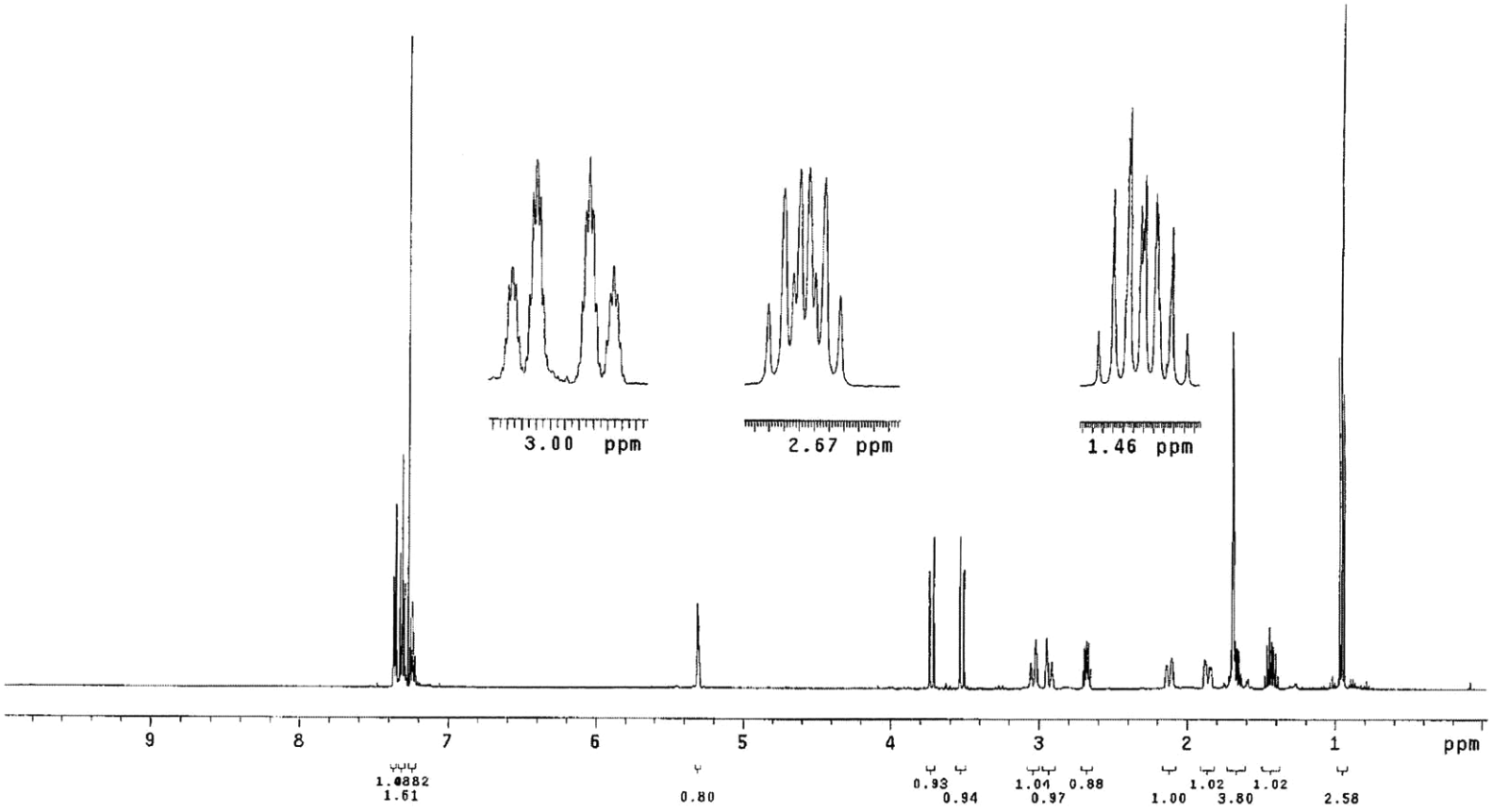
1-Benzyl-2-ethyl-4-methyl-1,2,3,6-tetrahydropyridine (191). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.13 mL, 0.096 g, 0.96 mmol, 2.0 equiv) in 2.5 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.53 M in hexanes, 0.38 mL, 0.96 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C

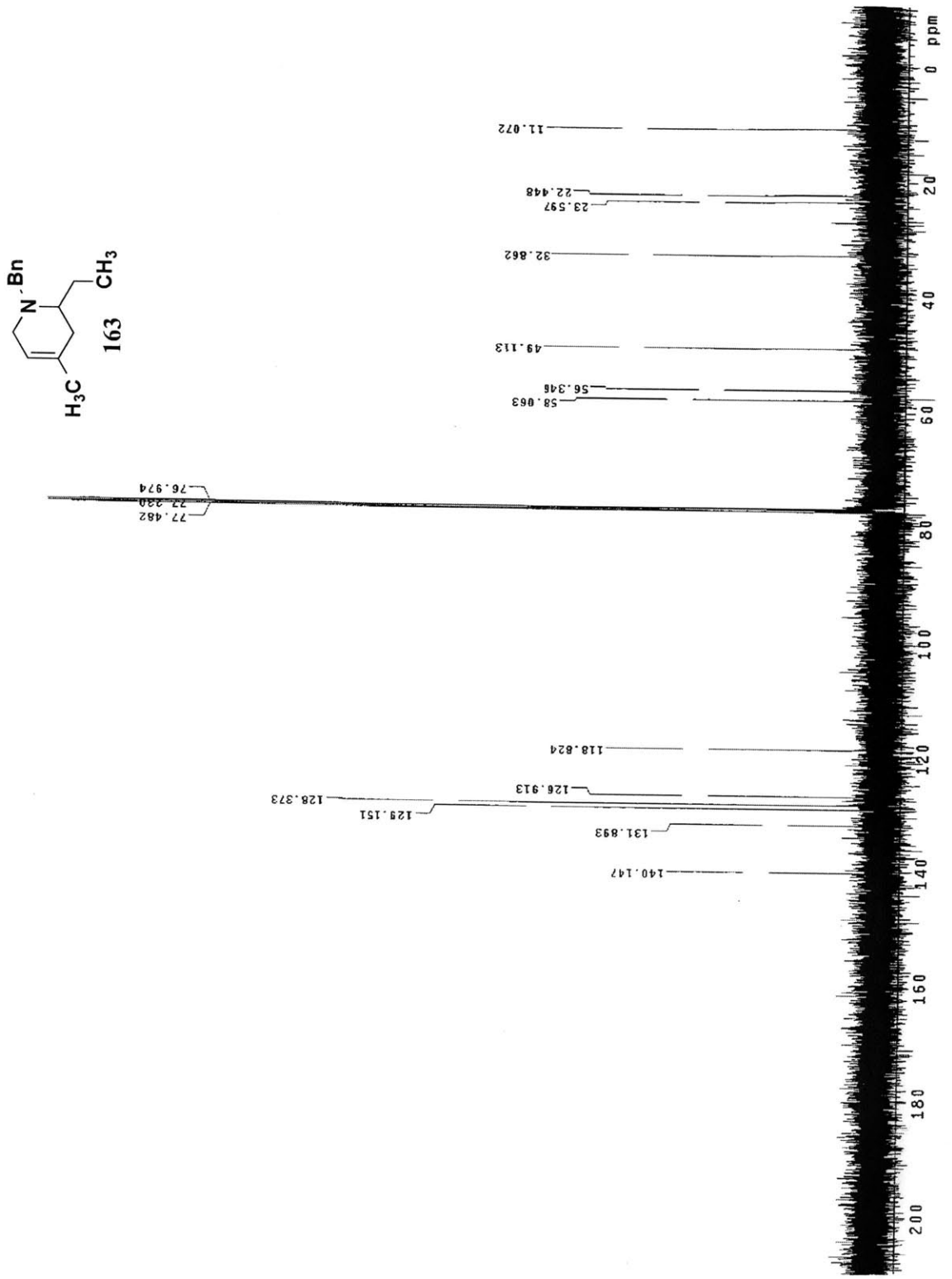
while a precooled (-78 °C) solution of amino nitrile **163** (0.102 g, 0.480 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.160 mL, 0.301 g, 1.92 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.124 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sodium cyanoborohydride (0.121 g, 1.92 mmol, 4.0 equiv), acetic acid (0.228 mL, 0.234 g, 3.84 mmol, 8.0 equiv), and 4 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min and then a solution of the amino nitrile prepared above in 2 mL of CH_3CN was added. The reaction mixture was stirred at rt for 90 min, diluted with 10 mL of 10% NaOH solution, and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered and concentrated to give 0.118 g of an orange oil. Purification by column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.074 g (72%) of **163** as a clear colorless oil with spectral data identical with that reported previously.


N
Bn
H3C
CH3

163


3.00 ppm
2.67 ppm
1.46 ppm
9
8
7
6
5
4
3
2
1
ppm
1.0882
1.61
0.80
0.93
0.94
1.04
0.97
0.88
1.00
1.02
3.80
1.02
2.58

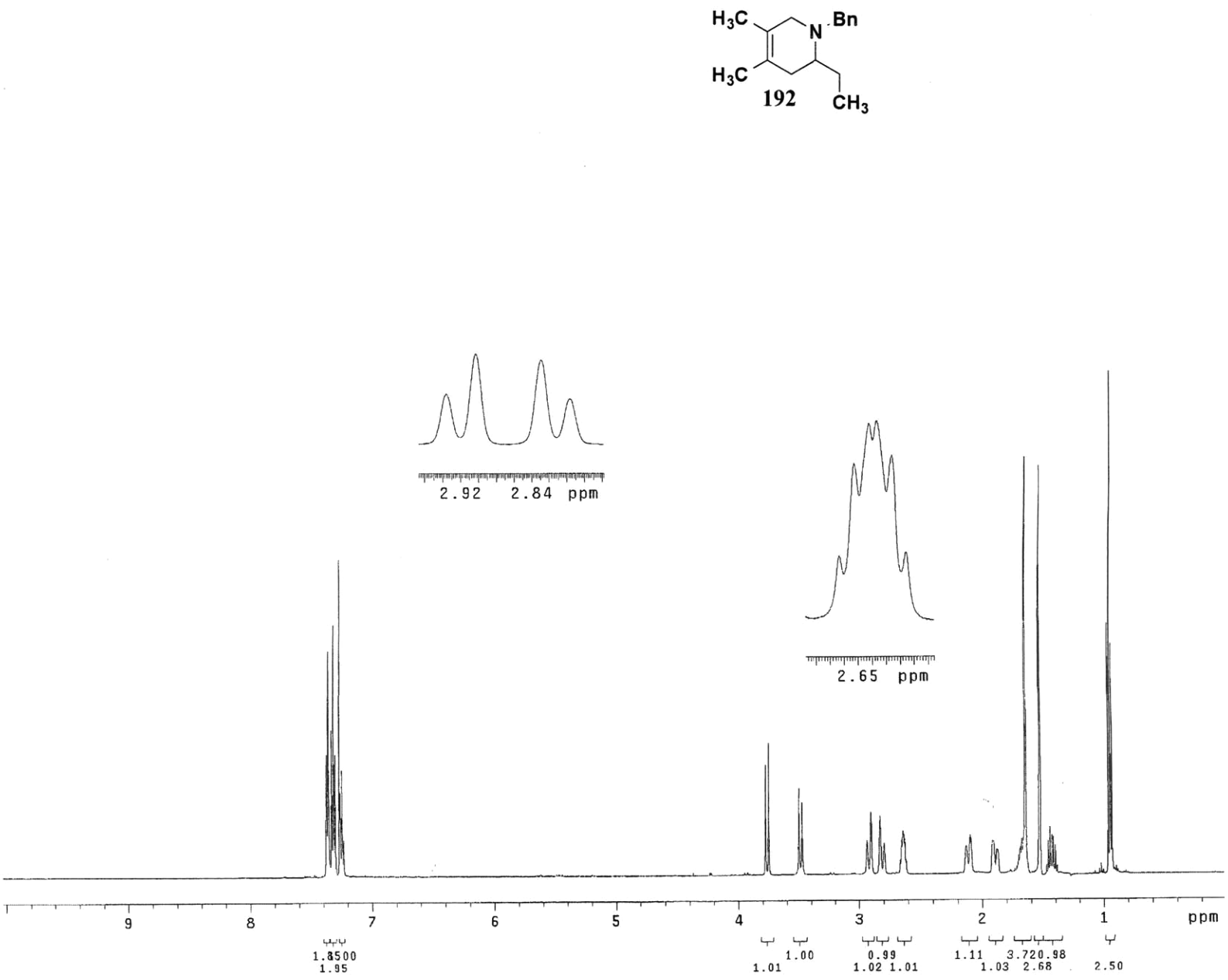

Bn
N
CH3
163
H3C
11.072
22.448
23.597
32.862
49.113
56.346
58.063
76.974
77.220
77.482
118.824
126.913
128.373
129.151
131.893
140.147
0
20
40
60
80
100
120
140
160
180
200
ppm

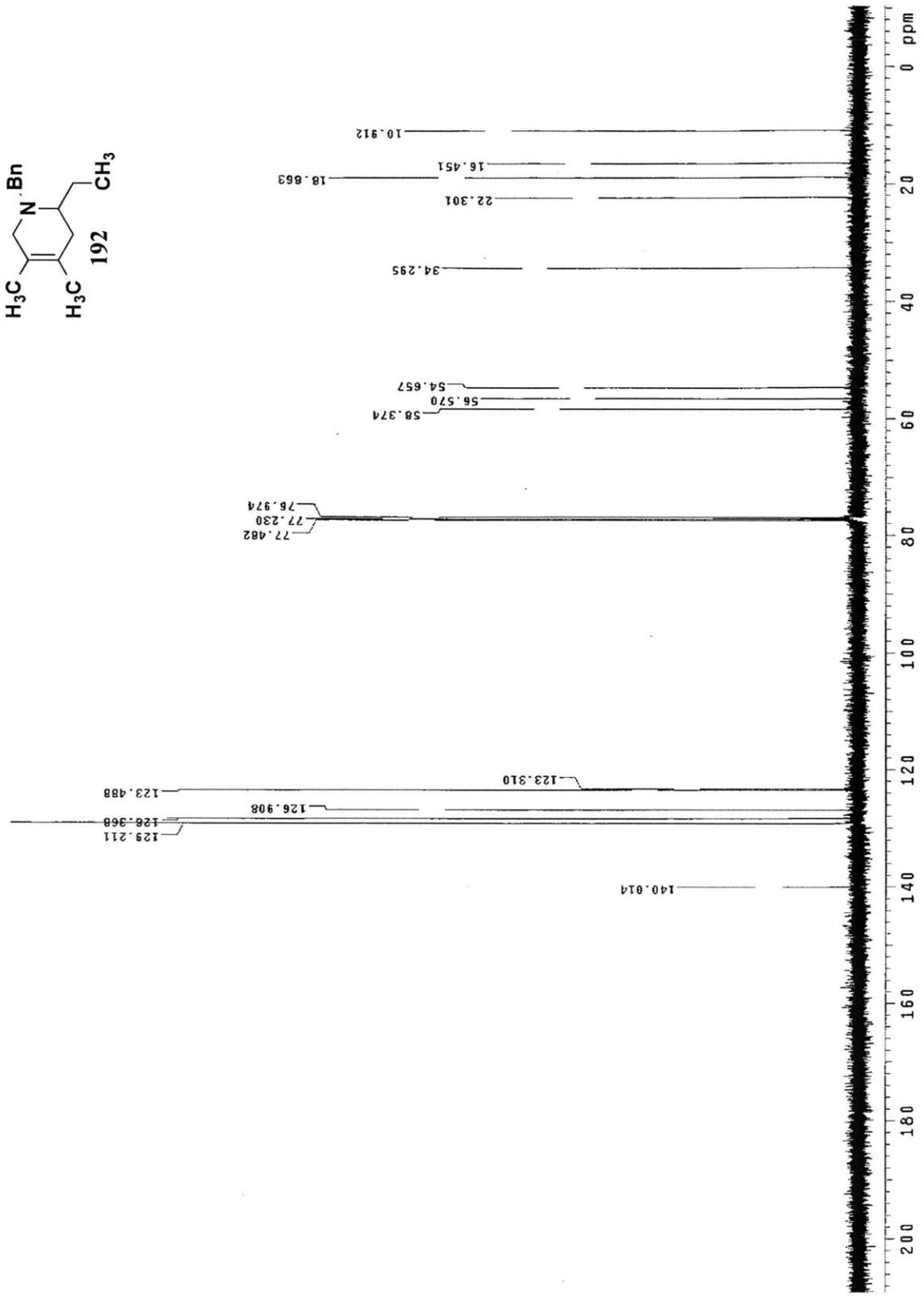
1-Benzyl-2-ethyl-4,5-dimethyl-1,2,3,6-tetrahydropyridine (192). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **164** (0.140 g, 0.620 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.61 M in Et_2O, 0.48 mL, 0.165 g, 1.24 mmol, 2.0 equiv) was added dropwise via syringe over 4 min. The reaction mixture is allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.152 g of an orange oil. Purification by column chromatography on 8 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.100 g (70%) of **192** as a yellow oil: IR (thin film) 3062, 3026, 2960, 2915, 2831, 1602, 1494, 1453, 1368, 1166, 1095, 1072, and 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2 H), 7.32 (t, J = 7.0 Hz, 2 H) 7.25 (t, J = 7.5 Hz, 1 H), 3.76 (d, J = 13.0 Hz, 1 H), 3.47 (d, J = 13.0 Hz, 1 H), 2.91 (d, J = 17.0 Hz, 1 H), 2.81 (d, J = 17.0 Hz, 1 H), 2.63 (m, 1 H), 2.10 (d, J = 18.0 Hz, 1 H), 1.89 (d, J = 18.0 Hz, 1 H), 1.66 (m, 1 H), 1.64 (s, 3 H), 1.52 (s, 3 H), 1.43 (m, 1 H), 0.94 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 129.2, 128.3, 126.9, 123.5, 123.3, 58.4, 56.6, 54.7, 34.3, 22.3, 18.9, 16.5, 10.9; HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{23}N$: 230.1903. Found: 230.1906.

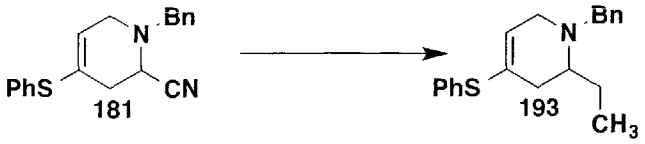
1-Benzyl-2-ethyl-4,5-dimethyl-1,2,3,6-tetrahydropyridine (192). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.11 mL, 0.075 g, 0.74 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.53 M in hexanes, 0.29 mL, 0.74 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled

at -78 °C while a precooled (-78 °C) solution of amino nitrile **164** (0.084 g, 0.37 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.123 mL, 0.232 g, 1.48 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.093 g of an orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sodium cyanoborohydride (0.093 g, 1.48 mmol, 4.0 equiv), acetic acid (0.175 mL, 0.180 g, 2.96 mmol, 8.0 equiv), and 4 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min and was then a solution of the amino nitrile prepared above in 2 mL of CH_3CN was added dropwise over 1 min. The reaction mixture was stirred at rt for 90 min, diluted with 10 mL of 10% NaOH solution, and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.101 g of an orange oil. Purification by column chromatography on 8 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.073 g (86%) of **192** as a yellow oil with spectral data identical with that reported previously.


H3C
N
Bn
H3C
CH3
192
2.92 2.84 ppm
2.65 ppm
9
8
7
6
5
4
3
2
1
ppm
1.8500
1.95
1.01
1.00
0.99
1.02 1.01
1.11
1.03
3.72
2.68
0.98
2.50


Bn
N
CH3
H3C
H3C
192
10.912
16.451
18.863
22.301
34.295
54.657
56.570
58.374
76.974
77.230
77.482
123.310
123.488
126.908
128.368
129.211
140.014
0 ppm
20
40
60
80
100
120
140
160
180
200

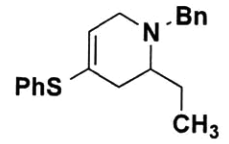


1-Benzyl-2-ethyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine (193). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **181** (0.129 g, 0.421 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.40 M in Et_2O, 0.351 mL, 0.112 g, 0.842 mmol, 3.0 equiv) was added dropwise via syringe over 4 min. The reaction mixture is allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 10 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.135 g of an orange oil. Purification by column chromatography on 14 g of Et_3N-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.108 g (83%) of **193** as a colorless oil: IR (thin film) 3029, 2929, 1582, 1453, 1365, 736, and 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.40 (m, 8 H), 7.23-7.26 (m, 2 H), 5.92 (br s, 1 H), 3.66 (AB q, J = 13.0 Hz, 2 H), 3.21 (dq, J = 17.5, 2.7, 1 H), 3.13 (dq, J = 17.5, 2.7, 1 H), 2.77 (dq, J = 7.5, 5.0 Hz, 1 H), 2.36 (dm, J = 17.5 Hz, 1 H), 2.05 (dm, J = 17.5 Hz, 1 H), 1.67 (m, 1 H), 1.45 (m, 1 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 134.5, 131.2, 129.6, 129.1, 129.0, 128.7, 128.5, 127.1, 127.0, 58.6, 56.3, 49.6, 31.8, 22.1, 11.1; HRMS (m/z) $[M+H]^+$ calcd for $C_{20}H_{23}NS$: 310.1624. Found: 310.1603.

1-Benzyl-2-ethyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine (193). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.067 mL, 0.048 g, 0.47 mmol, 1.1 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.31 M in hexanes, 0.205 mL, 0.474 mmol, 1.1 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **181** (0.132 g, 0.431 mmol, 1.0 equiv) in

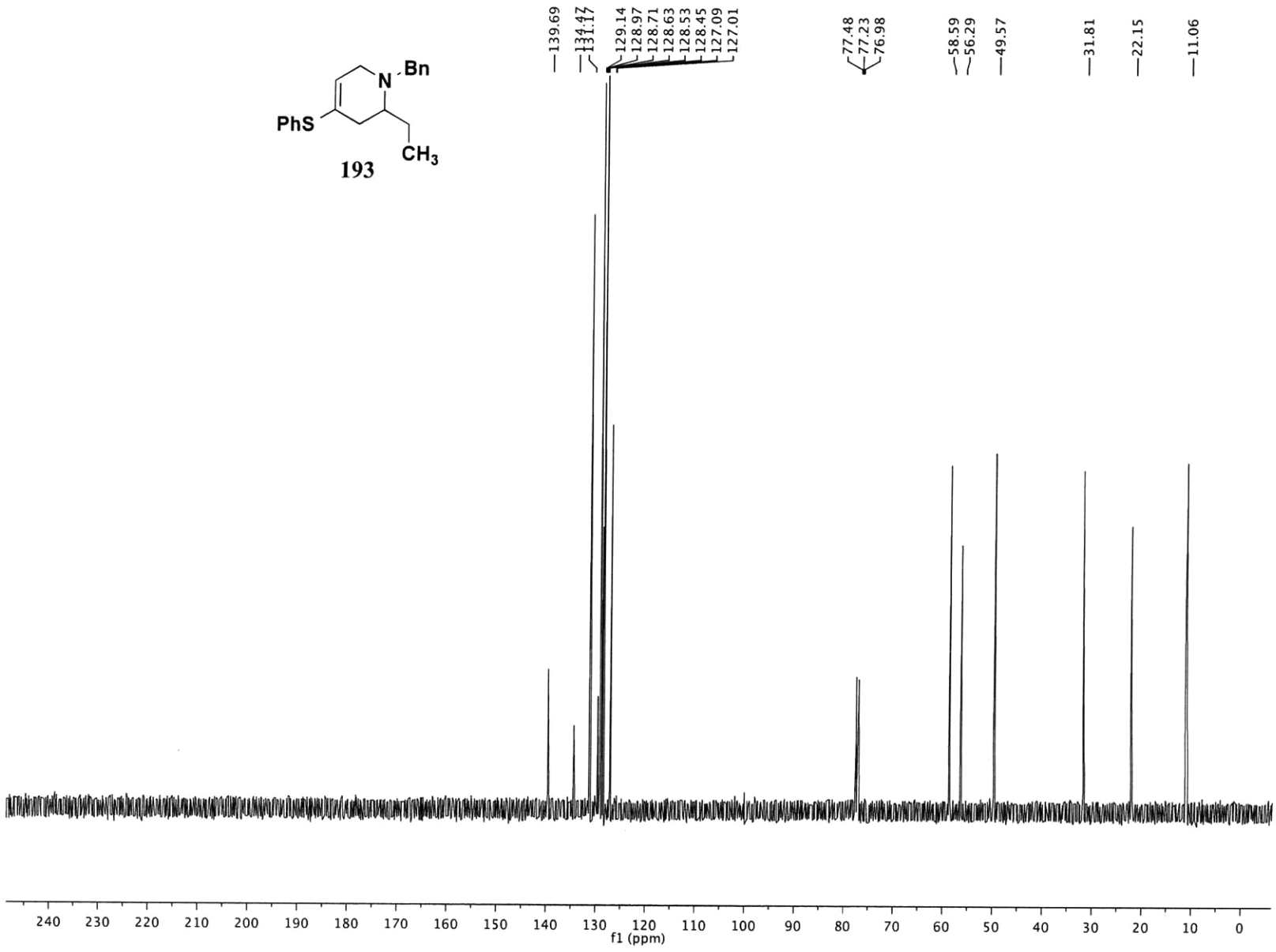
1 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.143 mL, 0.271 g, 1.72 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.148 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sodium cyanoborohydride (0.108 g, 1.72 mmol, 4.0 equiv), acetic acid (0.202 mL, 0.210 g, 3.35 mmol, 8.0 equiv), and 3 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min and then a solution of the amino nitrile prepared above in 2 mL of CH_3CN was added dropwise over 1 min. The reaction mixture was stirred at rt for 90 min, diluted with 10 mL of 10% NaOH solution, and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.159 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 1% MeOH-$CHCl_3$) afforded 0.095 g (71%) of **183** as a clear colorless oil with spectral data identical with that reported previously.

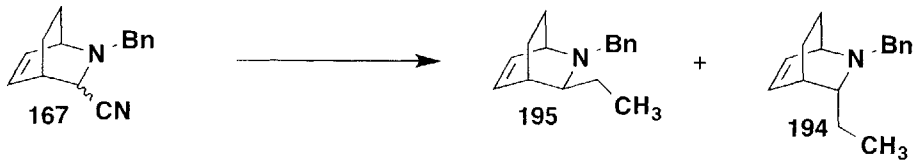

N
Bn
PhS
CH3

193

9
8
7
6
5
4
3
2
1
ppm
7.77
1.69
0.97
0.99
0.98
1.01
1.01
1.00
1.00
0.98
1.08
0.98
2.69


139.69
134.47
131.17
129.14
128.97
128.71
128.63
128.53
128.45
127.09
127.01
77.48
77.23
76.98
58.59
56.29
49.57
31.81
22.15
11.06
N
Bn
PhS
CH3
193
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2-Aza-2-benzyl-3-ethyl[2.2.2]bicyclooct-5-ene (194). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **167** (0.134 g, 0.57 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.61 M in Et_2O, 0.452 mL, 0.157 g, 1.18 mmol, 2.0 equiv) was added dropwise via syringe over 2 min. The reaction mixture was allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.147 g of an orange oil. Purification by column chromatography on 10 g of Et_3N-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.090 g (67%) of **194** as a colorless oil: IR (thin film) 3027, 2947, 1494, 1453, 1350, and 1138 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 7.8 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.24 (t, J = 7.0 Hz, 1 H), 6.40 (ddd, J = 8.0, 6.5, 1.5 Hz, 1 H), 6.18 (t, J = 7.0 Hz, 1 H), 3.77 (d, J = 13.0 Hz, 1 H), 3.59 (d, J = 13.0 Hz, 1 H), 3.17 (m, 1 H), 2.52 (m, 1 H), 2.18 (m, 1 H), 2.15 (m, 1 H), 1.56 (m, 1 H), 1.38 (tdd, J =11.5, 4.6, 3.0 Hz, 1 H), 1.14-1.27 (m, 2 H), 1.04 (dddd, J = 13.5, 11.5, 4.0, 2.0 Hz, 1 H), 0.83 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 136.1, 131.9, 129.3, 128.3, 127.0, 66.9, 58.0, 47.3, 33.5, 30.0, 24.8, 18.0, 11.3; HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{21}N$: 228.1747. Found: 228.1745.

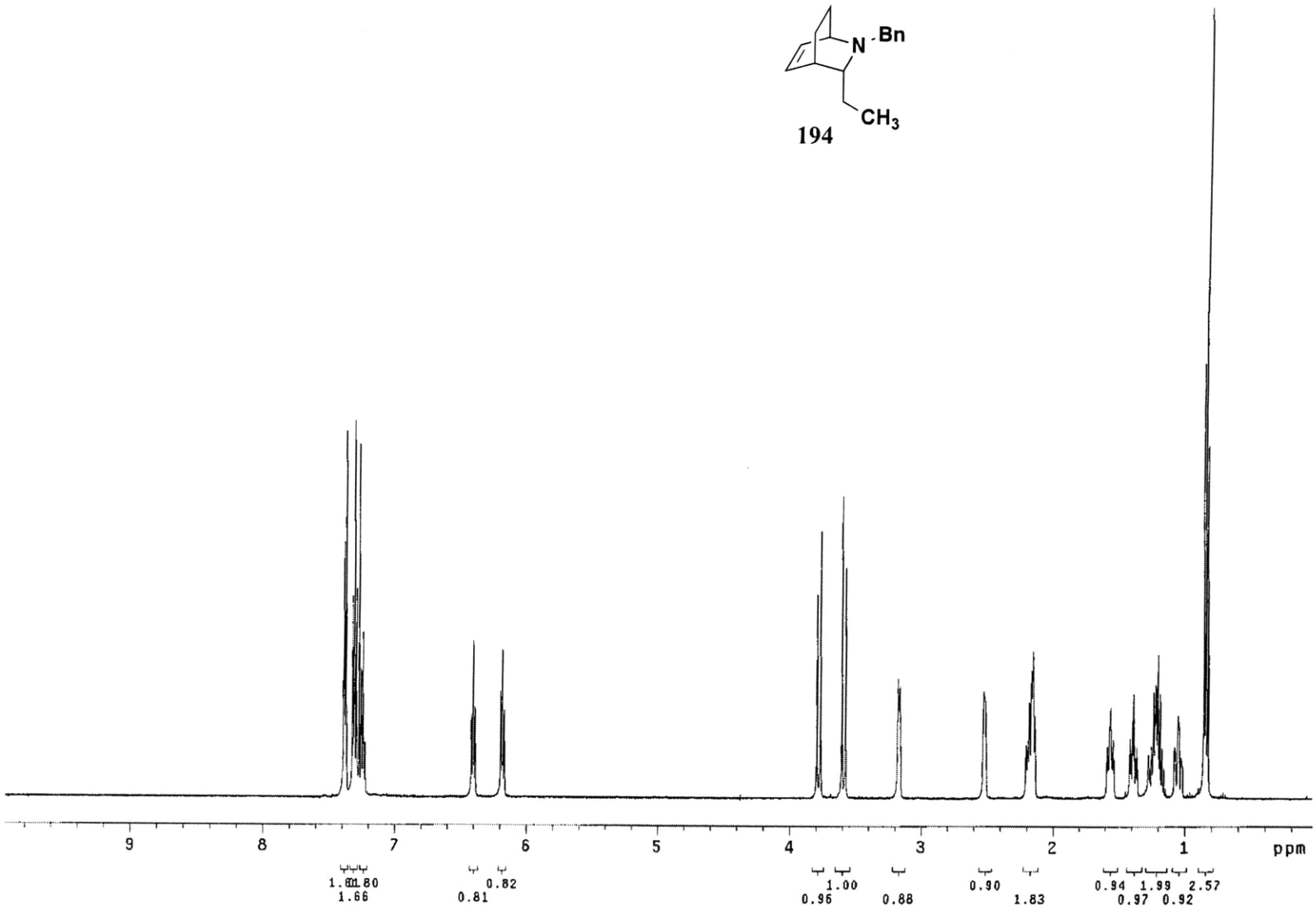


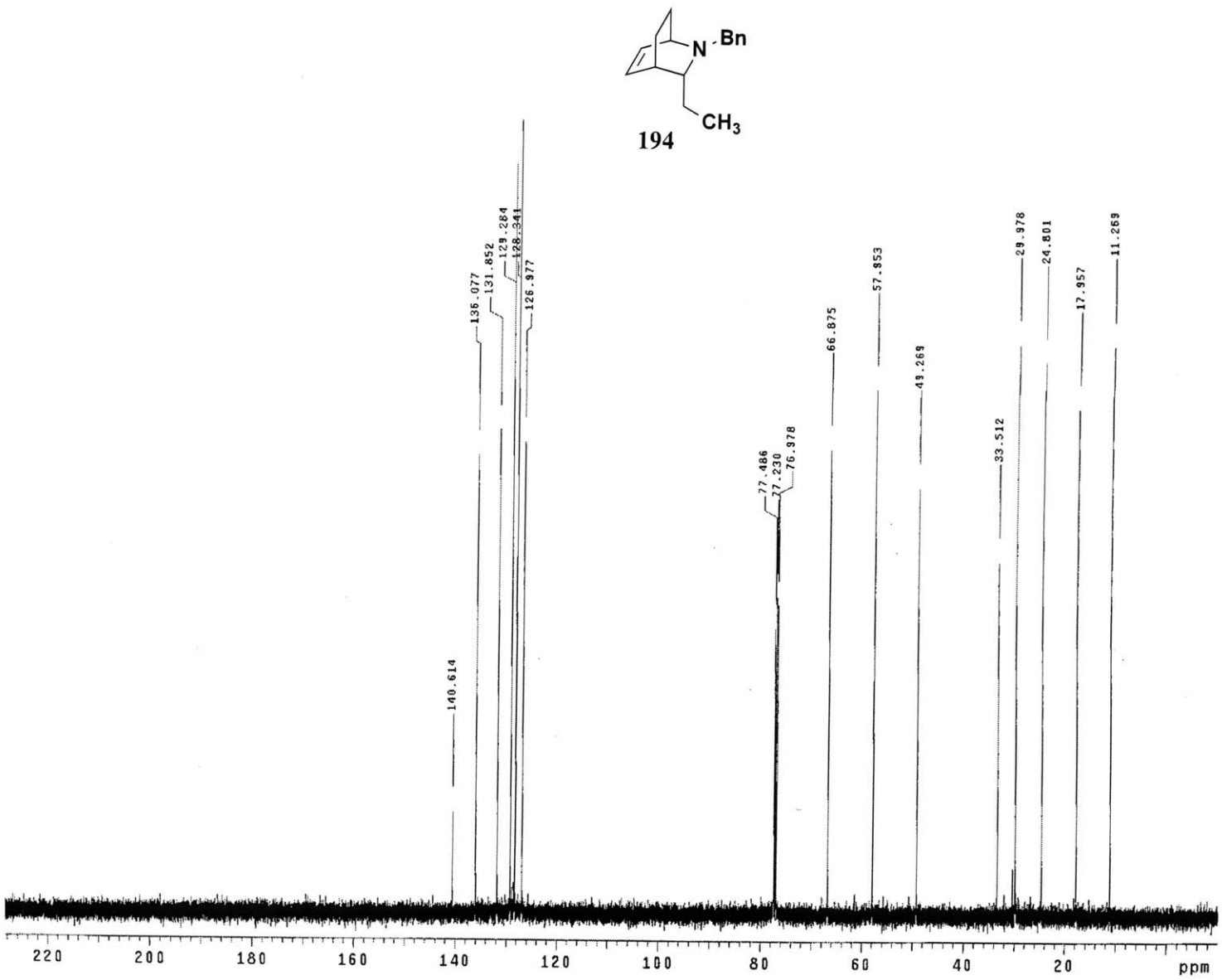
2-Aza-2-benzyl-3-ethyl[2.2.2]bicyclooct-5-ene (195 and **194).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of

diisopropylamine (0.150 mL, 0.108 g, 1.09 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.31 M in hexanes, 0.471 mL, 1.09 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **167** (0.122 g, 0.544 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.181 mL, 0.342 g, 2.18 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.132 g of an orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sodium cyanoborohydride (0.137 g, 2.18 mmol, 4.0 equiv), acetic acid (0.255 mL, 0.265 g, 4.35 mmol, 8.0 equiv), and 4 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min and was then a solution of the amino nitrile prepared above in 2 mL of CH_3CN was added dropwise over 1 min. The reaction mixture was stirred at rt for 90 min, diluted with 10 mL of 10% NaOH solution, and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.101 g of an orange oil. Purification by column chromatography on 12 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.107 g (86%) of **195** and **194** (75:25 ratio) as a yellow oil: IR (thin film) 3027, 2947, 1494, 1453, 1350, and 1138 cm^{-1}; For **195**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.0 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.24 (t, J = 7.0 Hz, 1 H), 6.54 (ddd, J =8.0, 7.0, 1.3 Hz, 1 H), 6.21 (dd, J = 8.0, 5.0 Hz, 1 H), 3.43 (d, J = 13.5 Hz, 1 H), 3.37 (d, J = 13.5 Hz, 1 H), 3.20 (m, 1 H), 2.42 (m, 1 H), 1.89 (t, J = 7.5 Hz, 1 H), 1.74 (m, 2 H), 1.61 (m, 1 H), 1.44 (m, 1 H), 1.20 (m, 1 H), 0.99 (m, 1 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 135.6, 131.1, 128.9, 128.3, 126.8, 65.5, 61.6, 50.5, 32.7, 27.2, 27.0, 16.5, 11.7; For **194**: spectral data was

identical with that reported previously. HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{21}N$: 228.1747. Found: 228.1745.


N
Bn
CH3
194
9
8
7
6
5
4
3
2
1
ppm
1.80
1.66
0.81
0.82
0.96
1.00
0.88
0.90
1.83
0.94
1.99
0.97
0.92
2.57


N
Bn
CH3
194
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131.852
129.284
128.341
126.977
77.486
77.230
76.978
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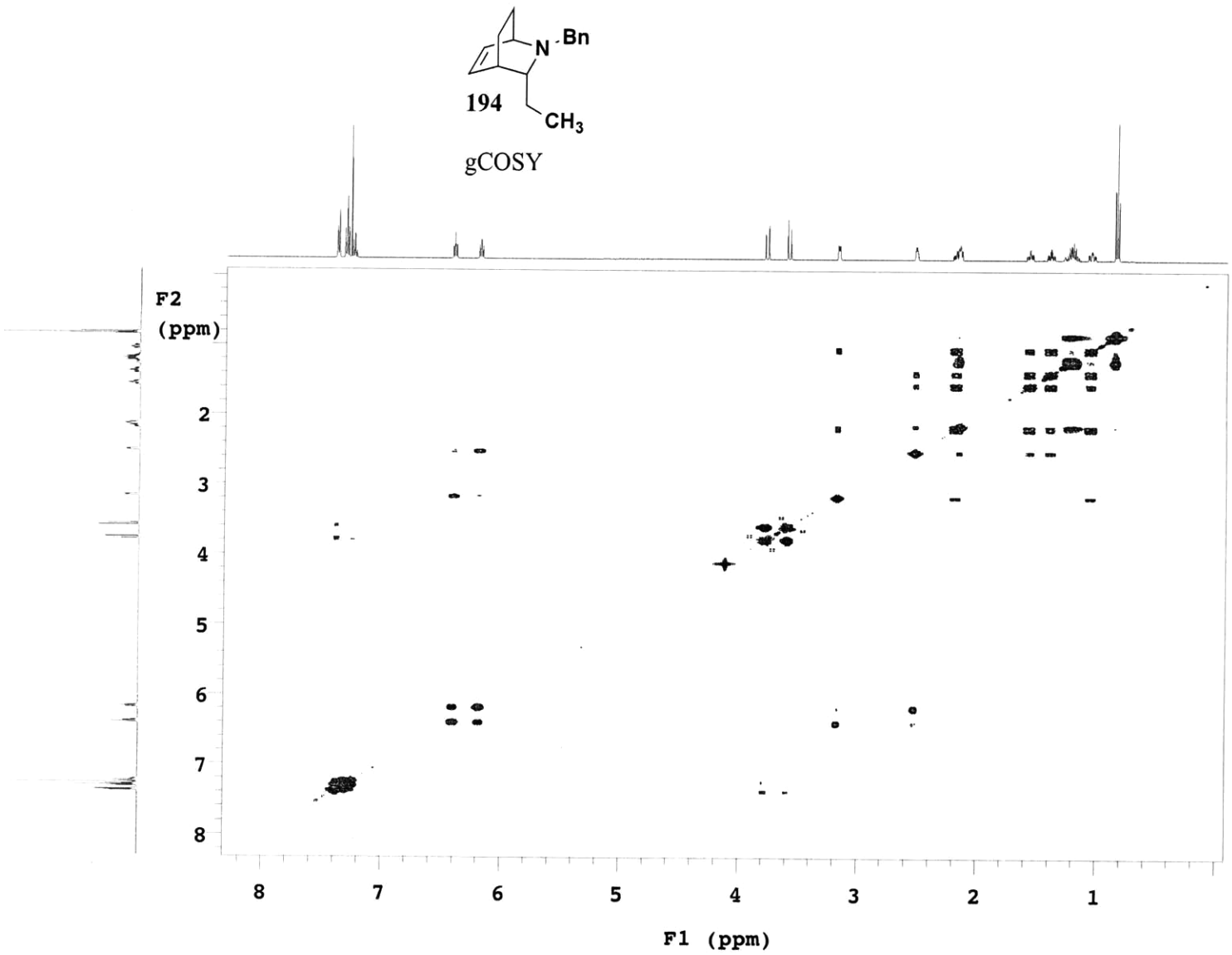
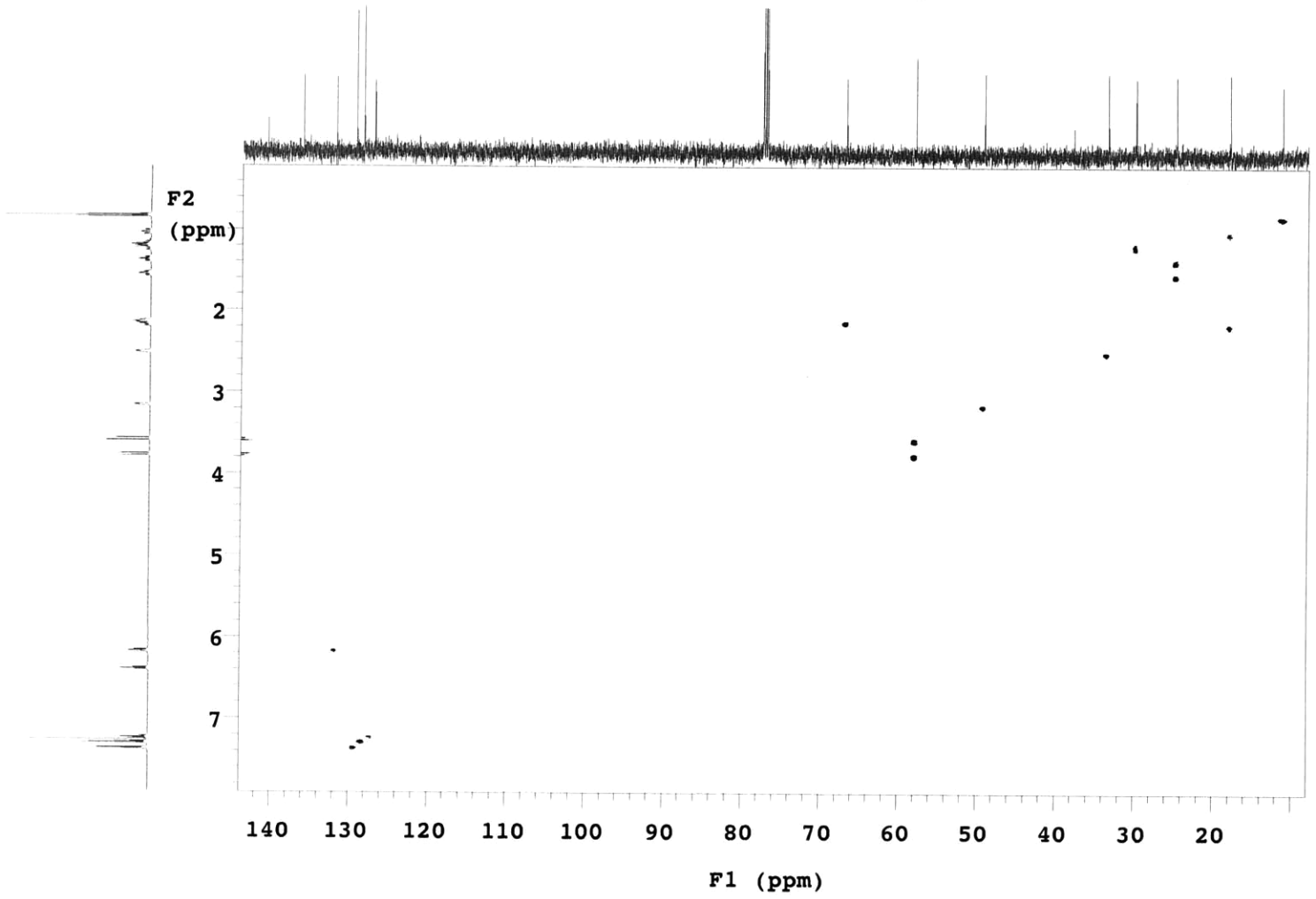
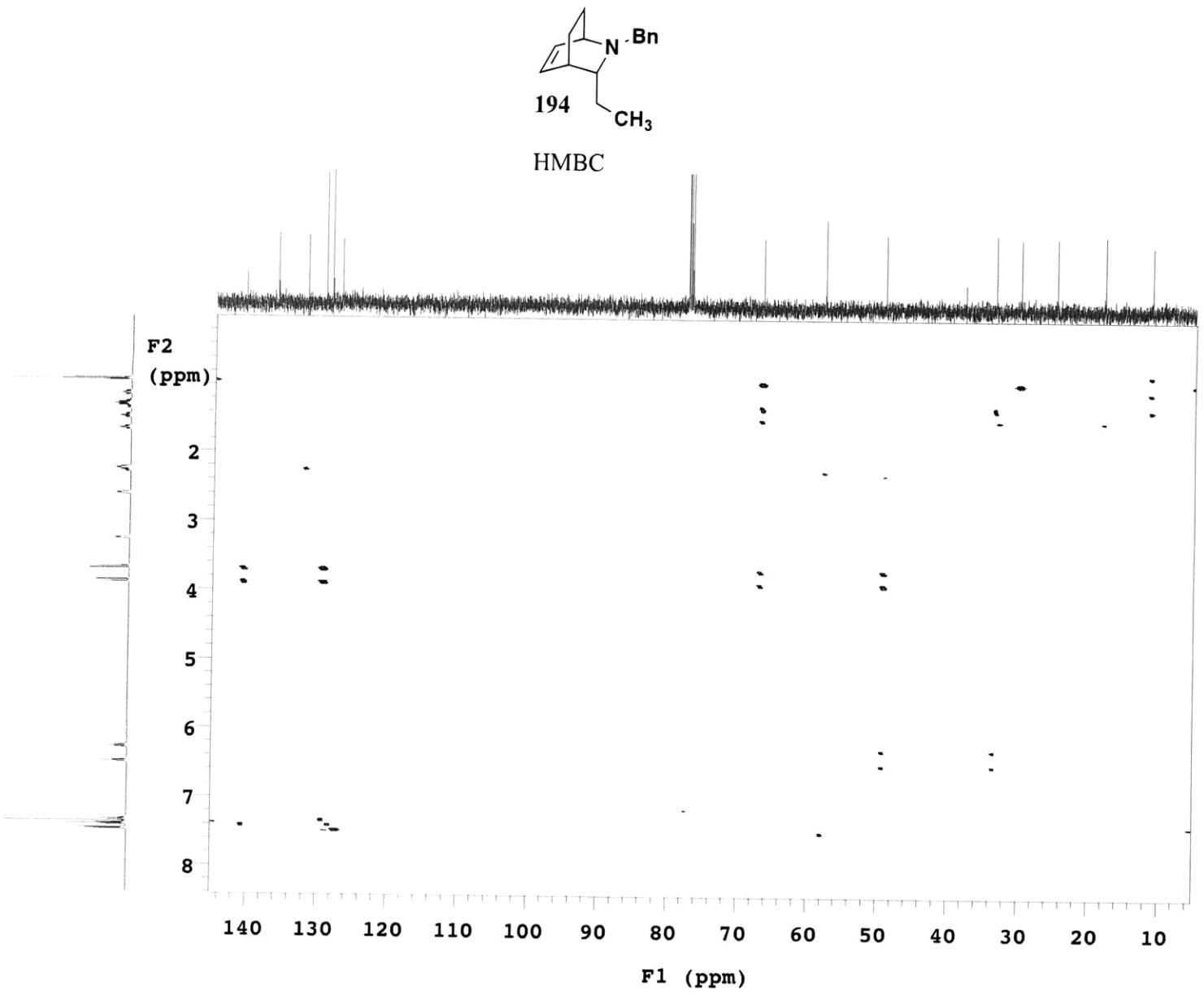
57.853
49.269
33.512
29.978
24.801
17.957
11.269
220
200
180
160
140
120
100
80
60
40
20
ppm

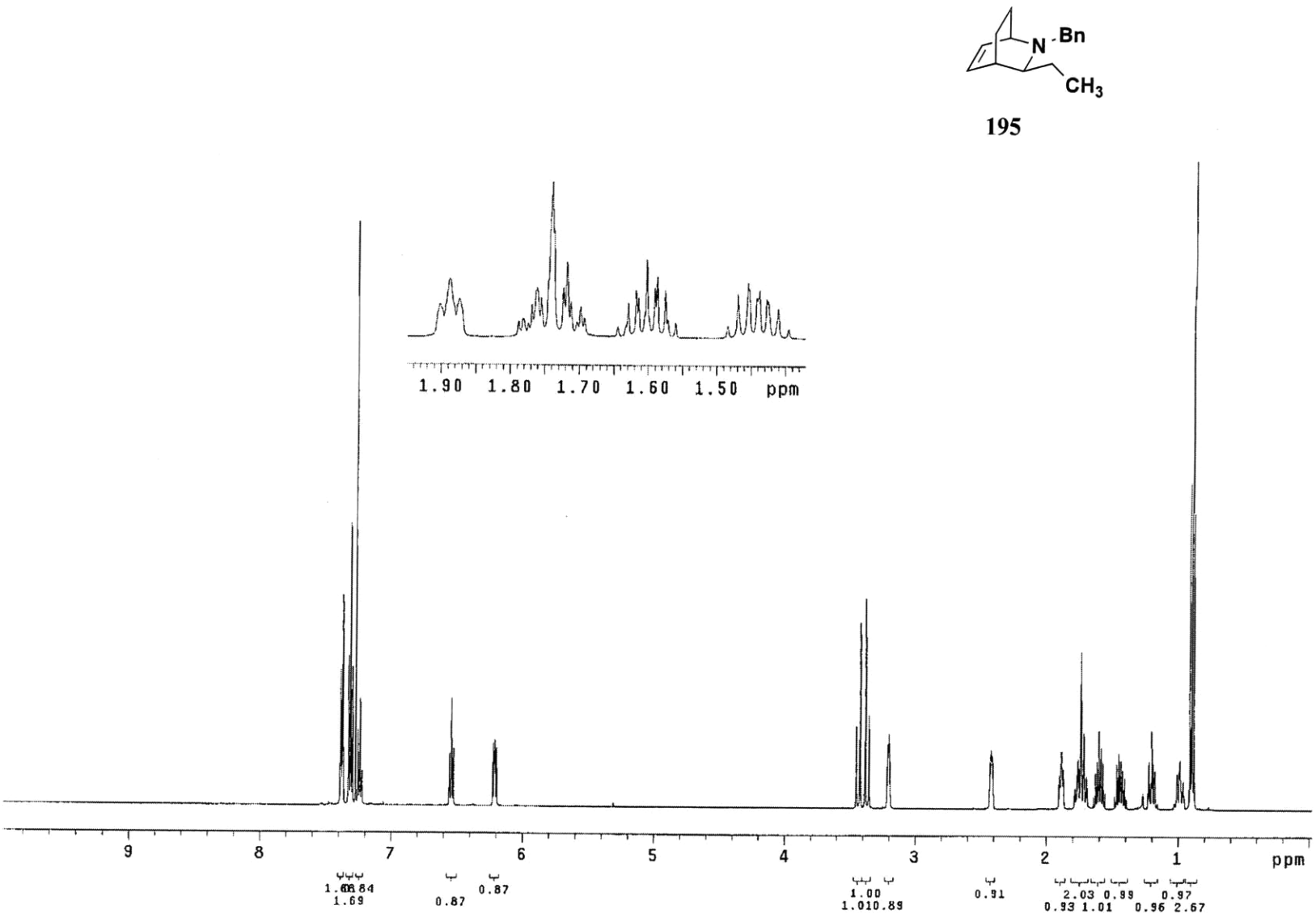

N
Bn
194
CH3
gCOSY
F2
(ppm)
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
F1 (ppm)

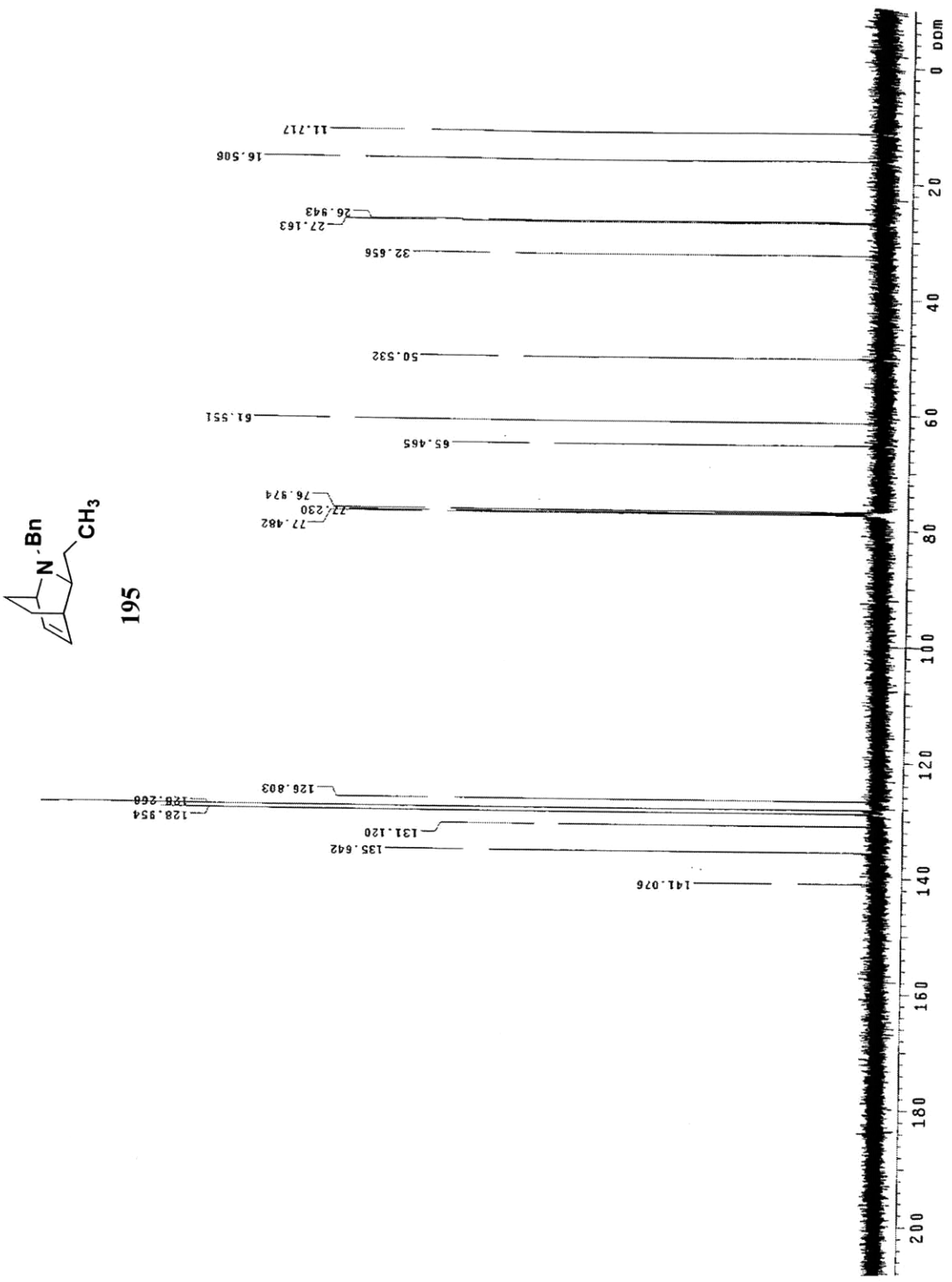
194

HSQC




N
Bn
194
CH3
HMBC
F2
(ppm)
2
3
4
5
6
7
8
140
130
120
110
100
90
80
70
60
50
40
30
20
10
F1 (ppm)


N
Bn
CH3
195
1.90 1.80 1.70 1.60 1.50 ppm
9 8 7 6 5 4 3 2 1 ppm
1.69
0.87
0.87
1.00
1.01
0.89
0.91
2.03
0.93
1.01
0.99
0.96
0.97
2.67


Bn
N
CH3
195
11.717
16.508
26.943
27.163
32.656
50.532
61.551
65.465
77.482
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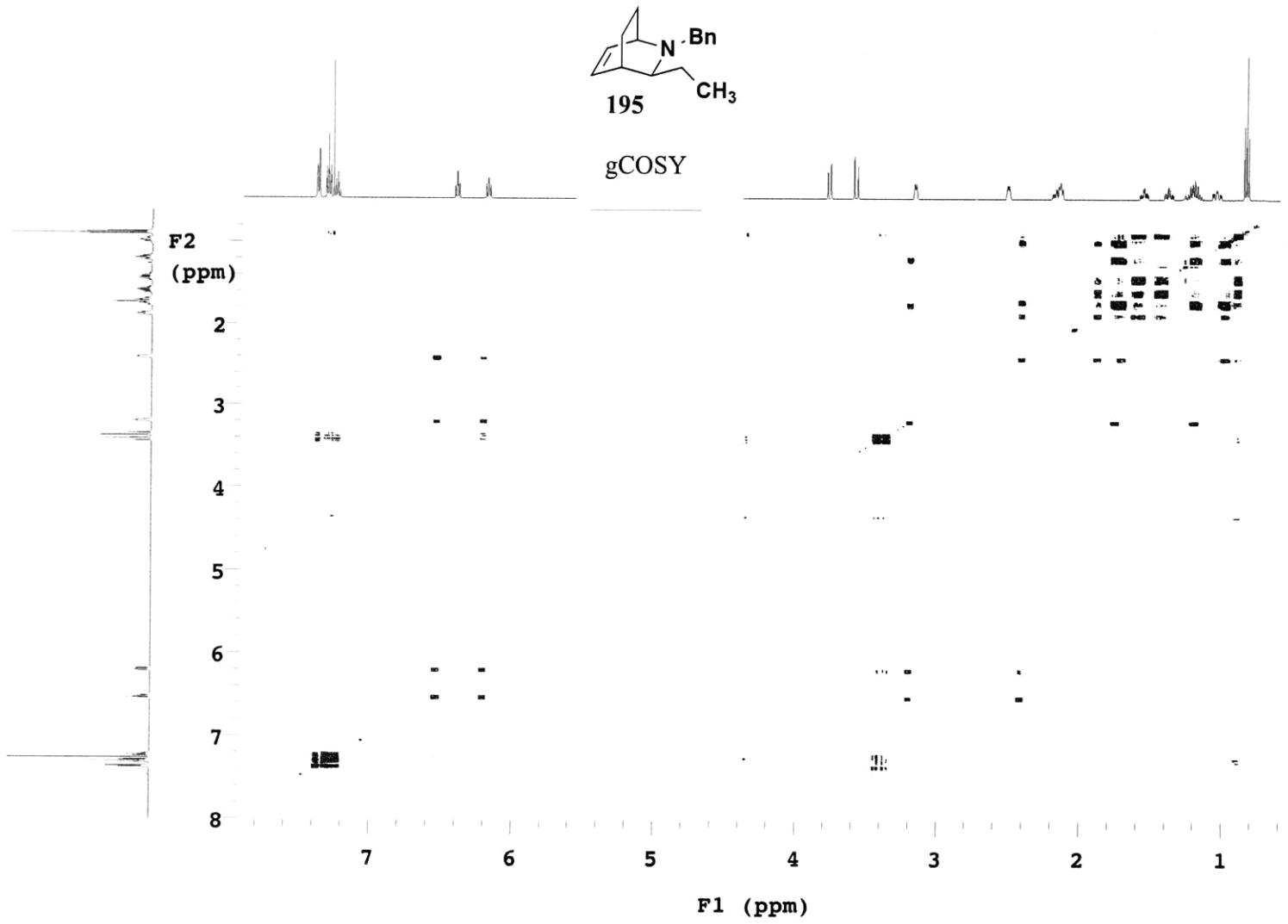
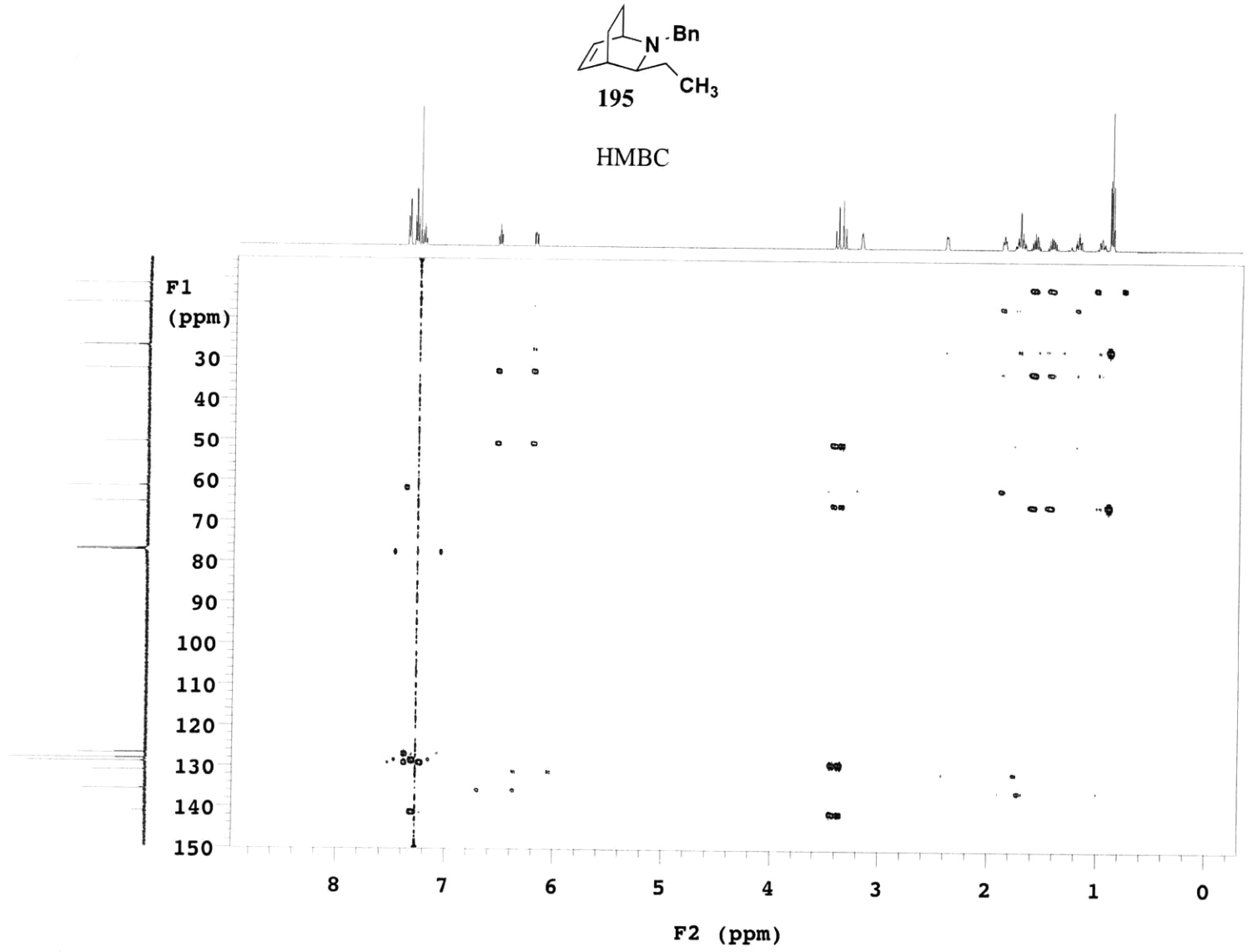
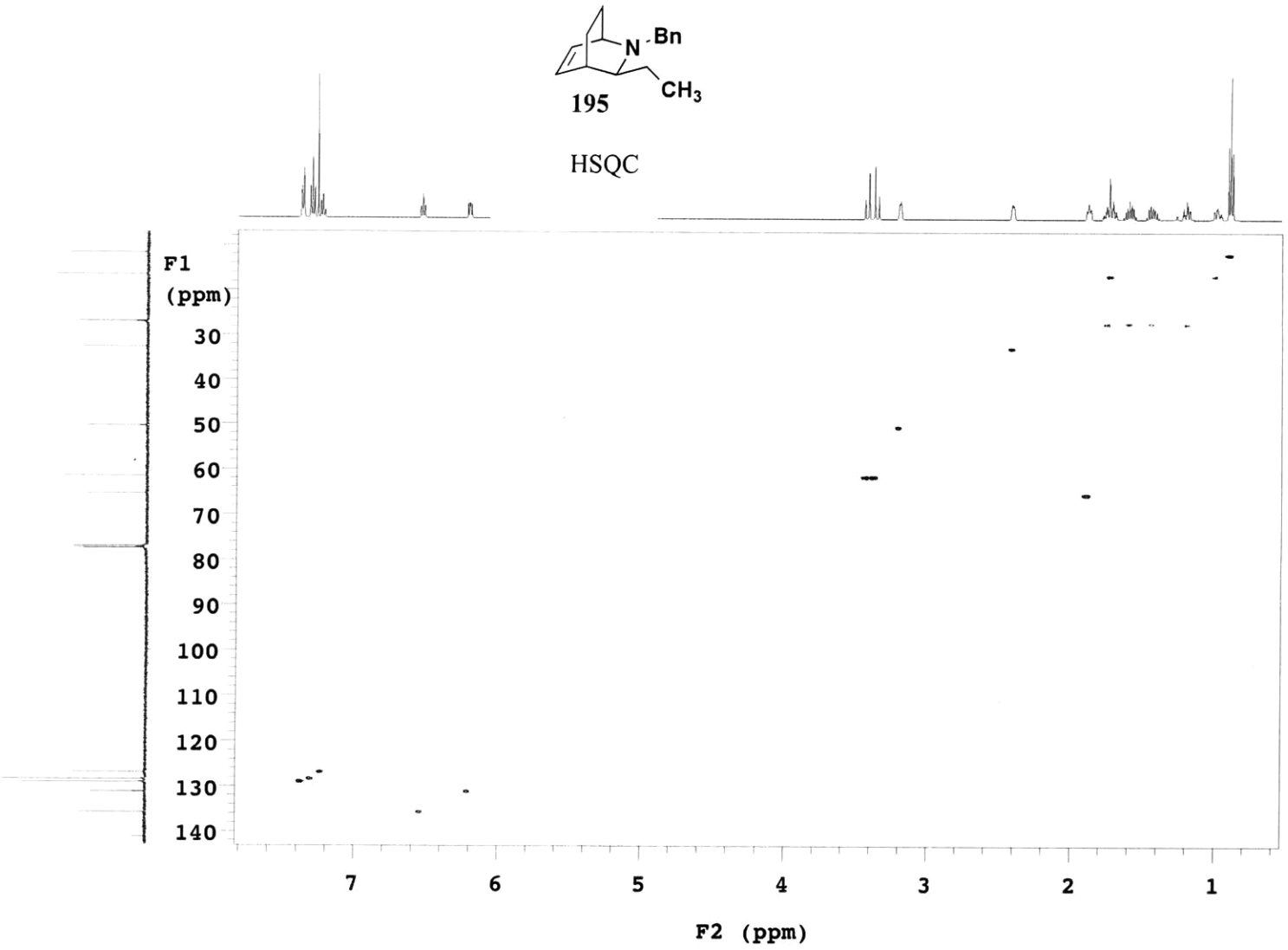
76.974
126.803
128.268
128.954
131.120
135.642
141.076
200
180
160
140
120
100
80
60
40
20
0 ppm


N
Bn
CH3
195
gCOSY
F2
(ppm)
2
3
4
5
6
7
8
7
6
5
4
3
2
1
F1 (ppm)


N
Bn
CH3
195
HMBC
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
8
7
6
5
4
3
2
1
0
F2 (ppm)


N
Bn
CH3
195
HSQC
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
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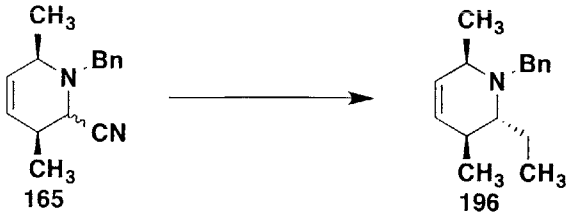
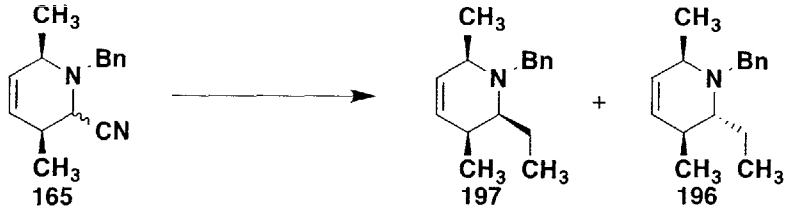
140
7
6
5
4
3
2
1
F2 (ppm)



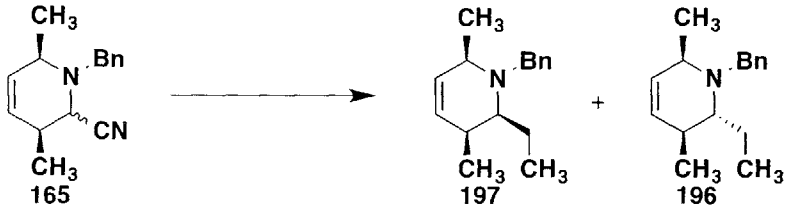
1-Benzyl-2-ethyl-3,6-dimethyl-1,2,3,6-tetrahydropyridine (196). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **165** (0.115g, 0.36 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.65 M in Et_2O, 0.38 mL, 0.136 g, 1.08 mmol, 2.0 equiv) was added dropwise via syringe over 4 min. The reaction mixture is allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.120 g of an orange oil. Purification by column chromatography on 12 g of Et_3N-deactivated silica gel (elution with 3% EtOAc-hexanes containing 1% Et_3N) afforded 0.101 g (86%) of **196** as a light yellow oil: IR (thin film) 3024, 2961, 2928, 2871, 1603, 1494, 1453, 1364, 1300, 1200, 1170, 1137, 1068, and 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 7.0 Hz, 2 H), 7.31 (t, J = 7.0 Hz, 2 H), 7.23 (t, J = 7.0 Hz, 1 H), 5.60 (ddd, J = 9.75, 3.5, 1.5 Hz, 1 H), 5.51 (ddd, J = 9.75, 3.0, 1.5 Hz, 1 H), 3.69 (d, J = 14.5 Hz, 1 H), 3.62 (d, J = 14.5 Hz, 1 H), 3.09 (m, 1 H), 2.40 (q, J = 7.0 Hz, 1 H), 2.07 (m, 1 H), 1.53 (m, 2 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 130.8, 130.5, 128.4, 128.2, 126.5, 60.5, 52.3, 51.6, 31.5, 20.8, 20.1, 19.8, 11.8; HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{23}N$: 230.1903. Found: 230.1907.



1-Benzyl-2-ethyl-3,6-dimethyl-1,2,3,6-tetrahydropyridine (197 and **196).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.12 mL, 0.089 g, 0.88 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.53 M in hexanes, 0.34 mL, 0.88 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **165** (0.100 g, 0.442 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.146 mL, 0.276 g, 1.76 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered and concentrated to give 0.114 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sodium cyanoborohydride (0.111 g, 1.76 mmol, 4.0 equiv), acetic acid (0.206 mL, 0.214 g, 3.52 mmol, 8.0 equiv), and 3 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min and then a solution of the amino nitrile prepared above in 5 mL of CH_3CN was added dropwise over 1 min. The reaction mixture was stirred at rt for 2 h, diluted with 10 mL of 10% NaOH solution, and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.120 g of a yellow oil. Purification by column chromatography on 15 g of Et_3N-deactivated silica gel (elution with 3% EtOAc-hexanes containing 1% Et_3N) afforded 0.073 g (73%) of **197** and **196** (80:20 *cis:trans* ratio

based on ^{1}H NMR analysis) as a colorless oil: IR (thin film) 3063, 3024, 2963, 2931, 2874, 1603, 1494, 1453, 1367, 1318, 1172, 1111, 1987, 1067, and 1027 cm^{-1}; For 2,6-*cis* isomer **197**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 5.66 (ddd, *J* = 10.0, 3.0, 2.5 Hz, 1 H), 5.51 (td, *J* = 10.0, 2.0 Hz, 1 H), 3.83 (d, *J* = 15.5 Hz, 1 H), 3.78 (d, *J* = 15.5 Hz, 1 H), 3.12 (m, 1 H), 2.61 (td, *J* = 7.5, 4.0 Hz, 1 H), 2.38 (m, 1 H), 1.50 (m, 1 H), 1.14 (m, 1 H), 1.12 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 130.4, 130.0, 128.2, 128.0, 126.4, 63.5, 58.1, 55.9, 30.2, 22.4, 22.2, 16.0 11.5: For 2,6-*trans* isomer **196** spectral data was identical with that reported previously. HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{23}N$: 230.1903. Found: 230.1907.

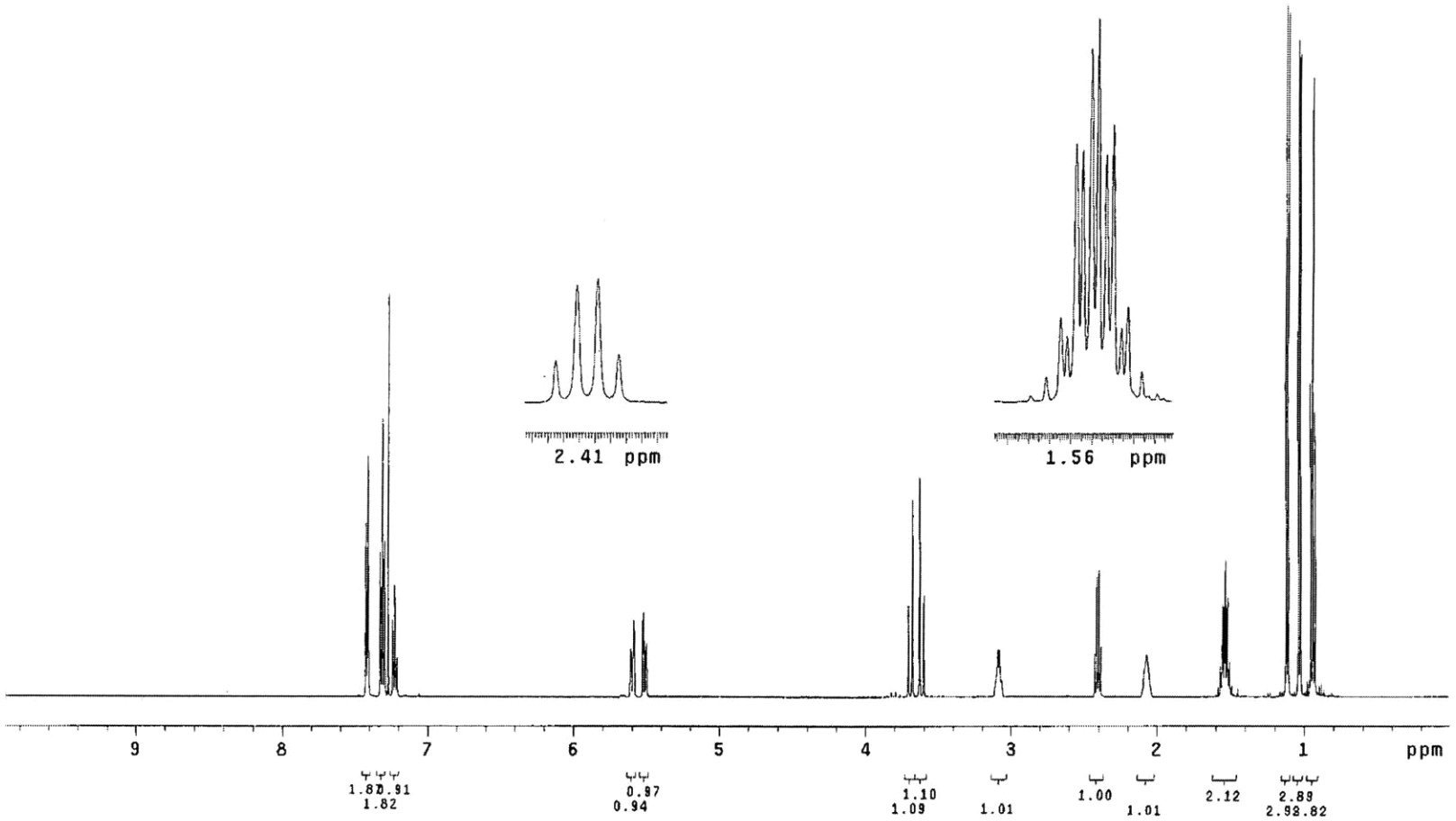


1-Benzyl-2-ethyl-3,6-dimethyl-1,2,3,6-tetrahydropyridine (197 and 196). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged a solution of diisopropylamine (0.14 mL, 0.097 g, 0.96 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled to 0 °C while *n*-BuLi (2.53 M in hexanes, 0.37 mL, 0.96 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **165** (0.109 g, 0.48mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.160 mL, 0.303 g, 1.93 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred for 1 h at 0 °C and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of saturated NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.123 g of yellow oil that was used immediately in the next step without further purification.

Approximately 20 mL of NH_3 was condensed at -78 °C into a 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and dewar condenser fitted with a rubber septum and argon inlet needle. Sodium metal (0.110 g, 4.80 mmol, 10.0 equiv) was then added and the resulting blue solution was stirred at -78 °C for 15 min. A solution of amino nitrile prepared above (0.123g, 0.482 mmol) in 2 mL of THF was then added, and then stirred at -78 °C for 5 min. Saturated NH_4Cl solution (10 mL) was added dropwise via syringe over 5 min. The rubber septum was removed from the dewar condenser and the reaction mixture was allowed to warm to rt over 3 h while the NH_3 evaporated. The resulting mixture was poured into 20 mL of saturated $NaHCO_3$ solution and extracted with three 20-mL portions of ether. The combined organic layers were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.107 g of a yellow oil. Purification by column chromatography on 15 g of silica gel (elution with hexanes containing 1% Et_3N) afforded 0.064 g (58%) of **197** and **196** (75:25 ratio based on ^1H NMR analysis) as a colorless oil with spectral data identical with that reported previously.


CH3
Bn
N
CH3
CH3

196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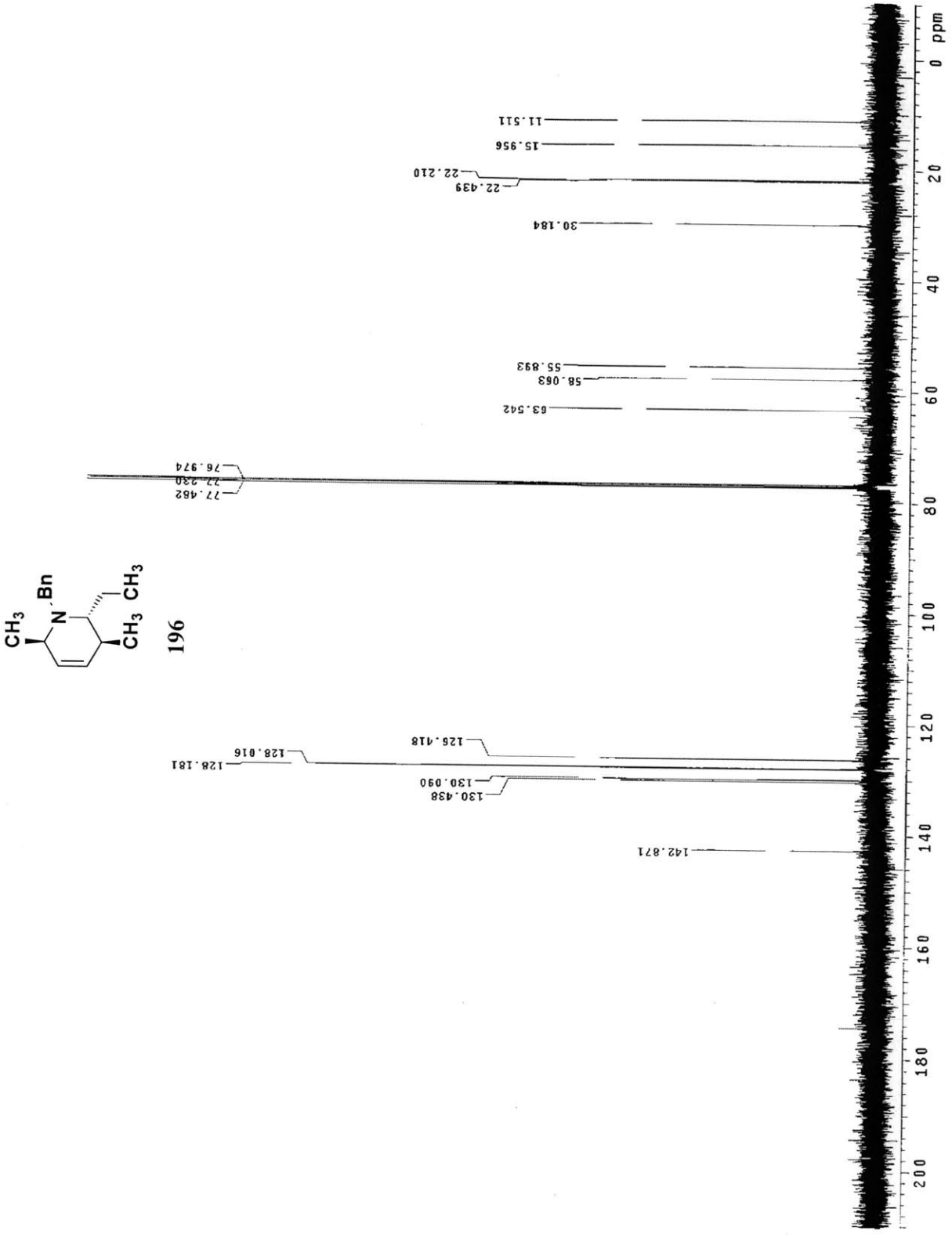
1.56 ppm
9
8
7
6
5
4
3
2
1
ppm
1.82
0.94
1.09
1.01
1.00
1.01
2.12
2.98.82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76.974
77.230
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128.181
130.090
130.438
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40
60
80
100
120
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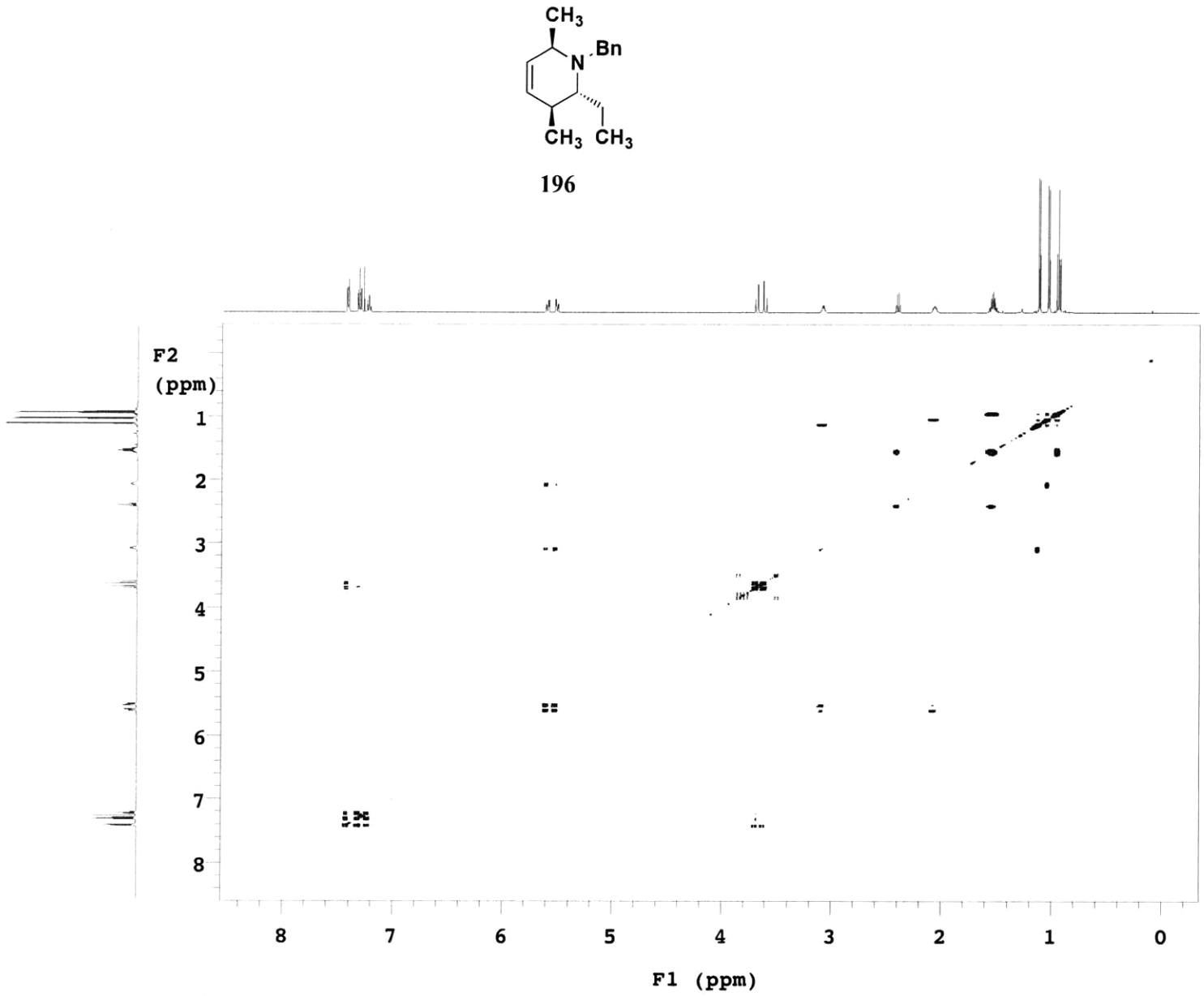
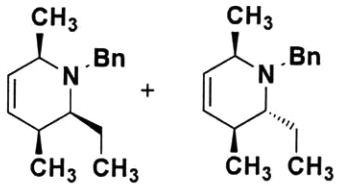
160
180
200
CH3
N
Bn
CH3
CH3

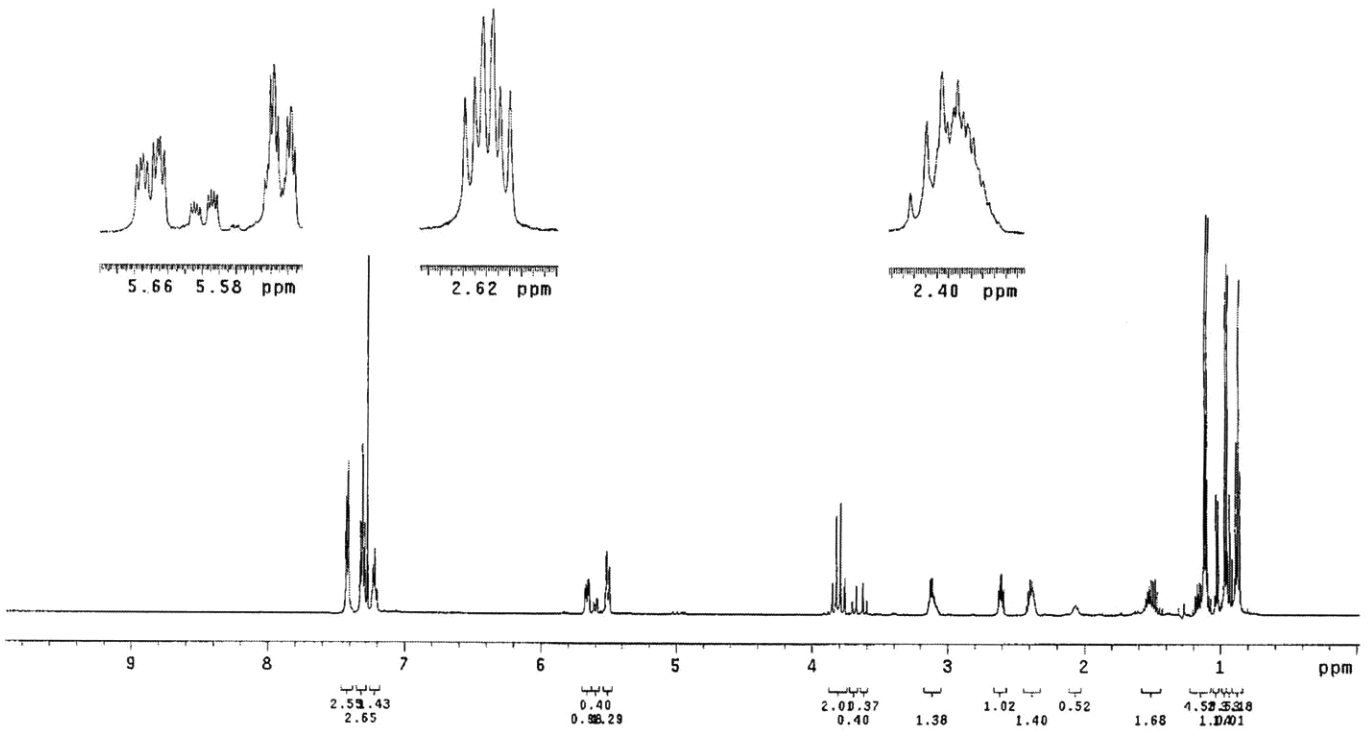
196



196


CH3
N
Bn
CH3
CH3
+
CH3
N
Bn
CH3
CH3

197 **196**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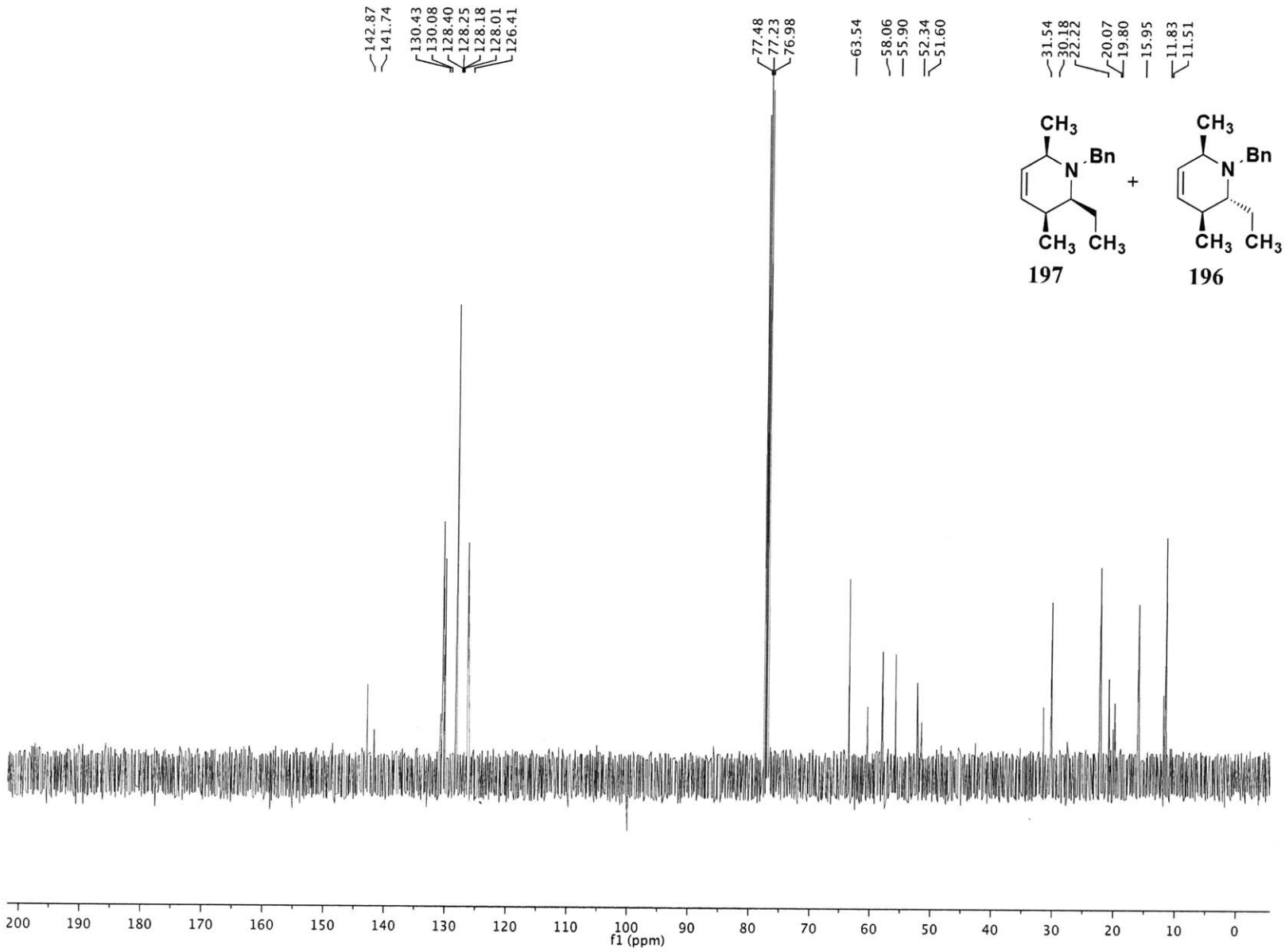
2.62 ppm
2.40 ppm
9
8
7
6
5
4
3
2
1
ppm


142.87
141.74
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130.08
128.40
128.25
128.18
128.01
126.41
77.48
77.23
76.98
63.54
58.06
55.90
52.34
51.60
31.54
30.18
22.22
20.07
19.80
15.95
11.83
11.51
CH3
Bn
N
CH3
CH3
+
CH3
Bn
N
CH3
CH3
197
196
200
190
180
170
160
150
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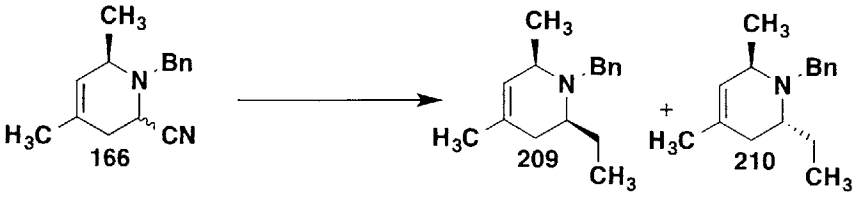
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



1-Benzyl-2-ethyl-4,6-dimethyl-1,2,3,6-tetrahydropyridine (209 and **210).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **166** (0.130 g, 0.576 mmol, 1.0 equiv) in 5 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.40 M in Et_2O, 0.479 mL, 0.153 g, 1.15 mmol, 3.0 equiv) was added dropwise via syringe over 4 min. The reaction mixture is allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.128 g of orange oil. Purification by column chromatography on 18 g of Et_3N-deactivated silica gel (elution with 2% EtOAc-hexanes containing 1% Et_3N) afforded 0.108 g (82%) of **209** and **210** (60:40 mixture of *cis:trans* isomers based on ^1H NMR analysis) as a light yellow oil: IR (thin film) 2962, 2921, 2869, 1602, 1492, 1452, 1474, 1136, 1056, and 1023 cm^{-1}; For 2,6-*cis* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J =7.0 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.21 (t, J = 7.5 Hz, 1 H), 5.25 (m, 1 H), 3.77 (d, J = 15.5 Hz, 1 H), 3.71 (d, J = 15.5 Hz, 1 H), 3.30 (m, 1 H), 2.72 (tdd, J = 9.0, 7.0, 5.0 Hz, 1 H), 2.06 (d, J = 16.5 Hz, 1 H), 1.80 (dd, J = 16.8, 6.5 Hz, 1 H), 1.71 (s, 3 H), 1.70 (m, 1 H), 1.26 (m, 1 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 131.2, 128.2, 126.4, 125.1, 60.0, 55.6, 54.0, 32.8, 27.2, 23.6, 21.4, 11.7; For 2,6-*trans* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.0 Hz, 2 H), 7.30 (m, 2 H), 7.22 (t, J = 7.5 Hz, 2 H), 7.22 (t, J = 7.5 Hz, 1 H), 5.27 (m, 1 H), 3.69 (d, J = 14.0 Hz, 1 H), 3.43 (d, J = 14.0 Hz, 1 H), 3.07 (m, 1 H), 2.86 (m, 1 H), 1.83 (m, 2 H), 1.61 (m, 1 H), 1.70 (s, 3 H), 1.45 (m, 1 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.97 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 131.8, 128.5,

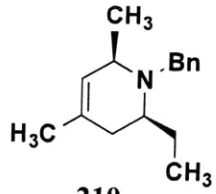
128.3, 126.5, 124.7, 53.5, 52.7, 50.5, 31.9, 24.1, 23.6, 20.1, 11.7; HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{23}N$: 230.1903. Found: 230.1901.

1-Benzyl-2-ethyl-4,6-dimethyl-1,2,3,6-tetrahydropyridine (209 and **210).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.13 mL, 0.094 g, 0.93 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.53 M in hexanes, 0.37 mL, 0.93 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **166** (0.107 g, 0.473 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.155 mL, 0.293 g, 1.87 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.121 g of orange oil that was used immediately in the next step without further purification.

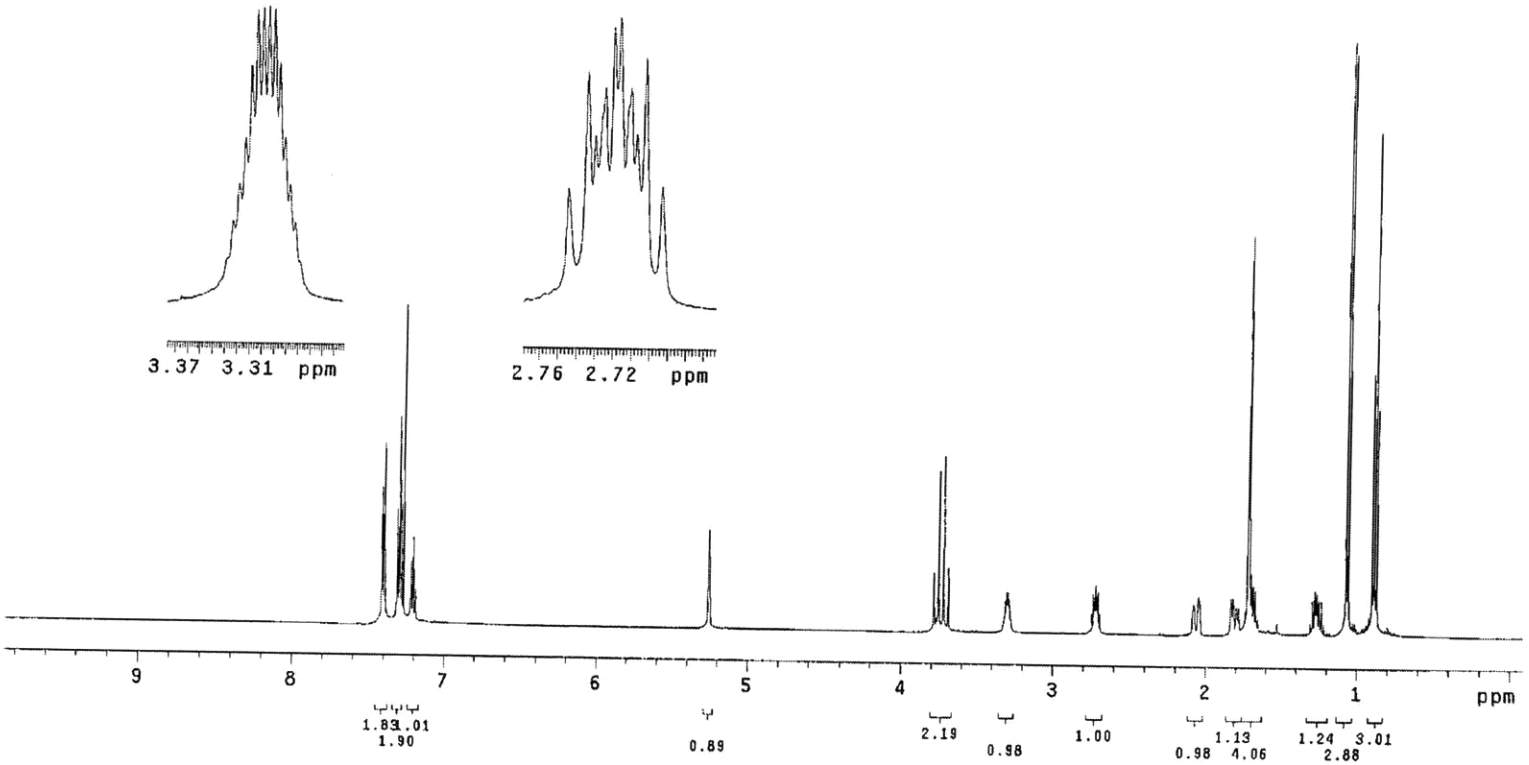
A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sodium cyanoborohydride (0.118 g, 1.87 mmol, 4.0 equiv), acetic acid (0.219 mL, 0.228 g, 3.76 mmol, 8.0 equiv), and 3 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min and then a solution of the amino nitrile prepared above in 3 mL of CH_3CN was added dropwise over 1 min. The reaction mixture was stirred at rt for 90 min, diluted with 10 mL of 10% NaOH solution, and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.100 g of a yellow oil. Purification by column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.052 g (48%) of **209** and **210** as a clear colorless oil with spectral data identical with that reported previously.

1-Benzyl-2-ethyl-4,6-dimethyl-1,2,3,6-tetrahydropyridine (209 and **210).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.149 mL, 0.107 g, 1.06 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.60 M in hexanes, 0.408 mL, 1.06 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **166** (0.120 g, 0.530 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.176 mL, 0.333 g, 2.12 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.136 g of yellow oil that was used immediately in the next step without further purification.

Approximately 20 mL of NH_3 was condensed at -78 °C into a 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and a Dewar condenser fitted with a rubber septum and argon inlet needle. Sodium metal (0.121 g, 5.30 mmol, 10.0 equiv) was added and the resulting blue solution was stirred at -78 °C for 15 min. A solution of the amino nitrile prepared above in 2 mL of THF was then added, and the resulting mixture was stirred at -78 °C for 5 min. Satd NH_4Cl solution (10 mL) was added dropwise via syringe over 5 min. The rubber septum was removed from the Dewar condenser and allowed to warm to rt over 3 h while the NH_3 evaporated. The resulting mixture was poured into 20 mL of satd $NaHCO_3$ solution and extracted with three 20-mL portions of ether. The combined organic layers were washed with 30 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.122 g of yellow oil. Purification by column chromatography on 15 g of Et_3N-deactivated silica gel (elution hexanes containing 1% Et_3N) afforded 0.080 g (66%) of **209** and **210** (65:35 ratio based on ^1H NMR analysis) as a light yellow oil with spectral data identical with that reported previously


CH3
Bn
N
H3C
CH3

210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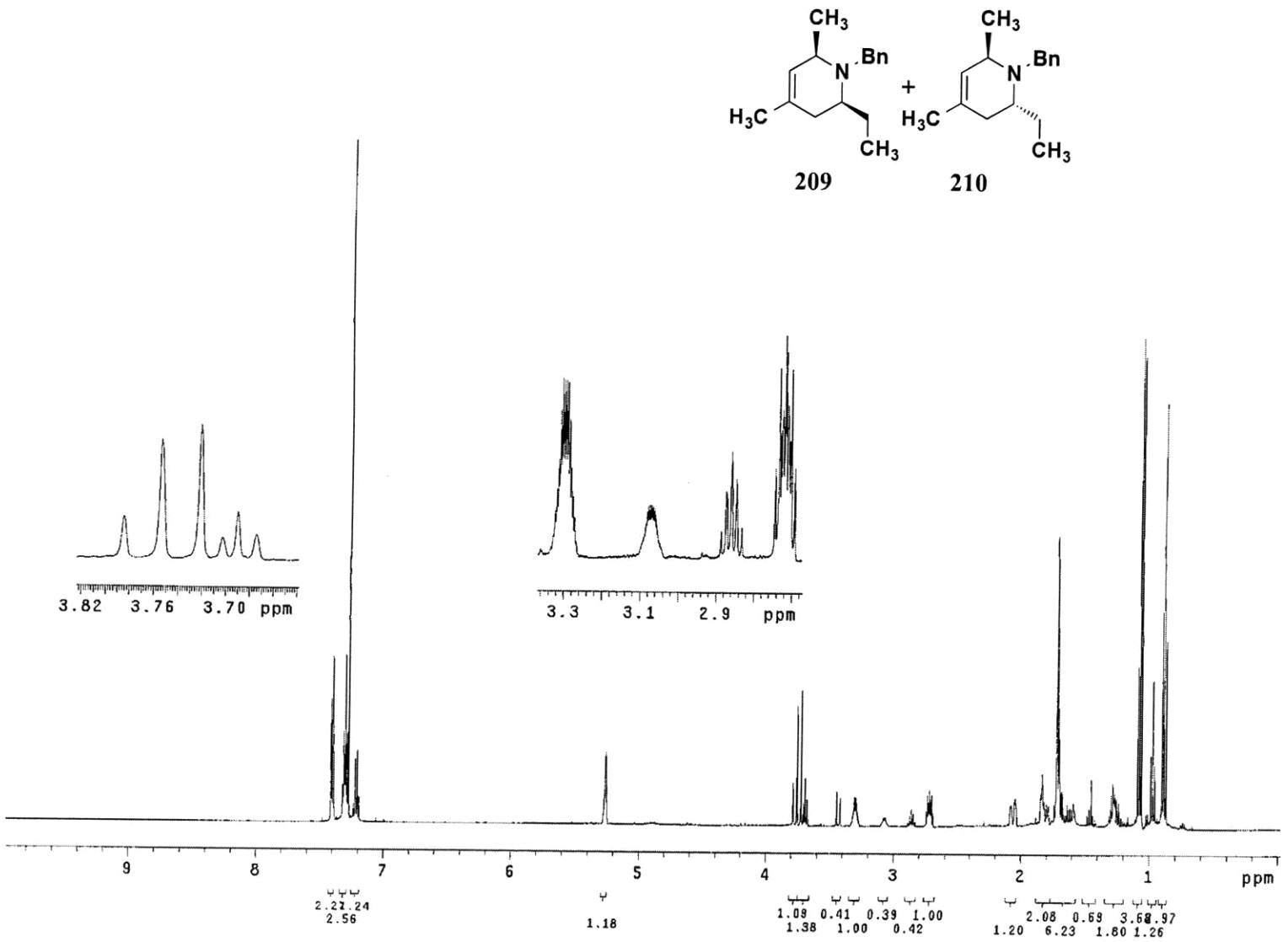
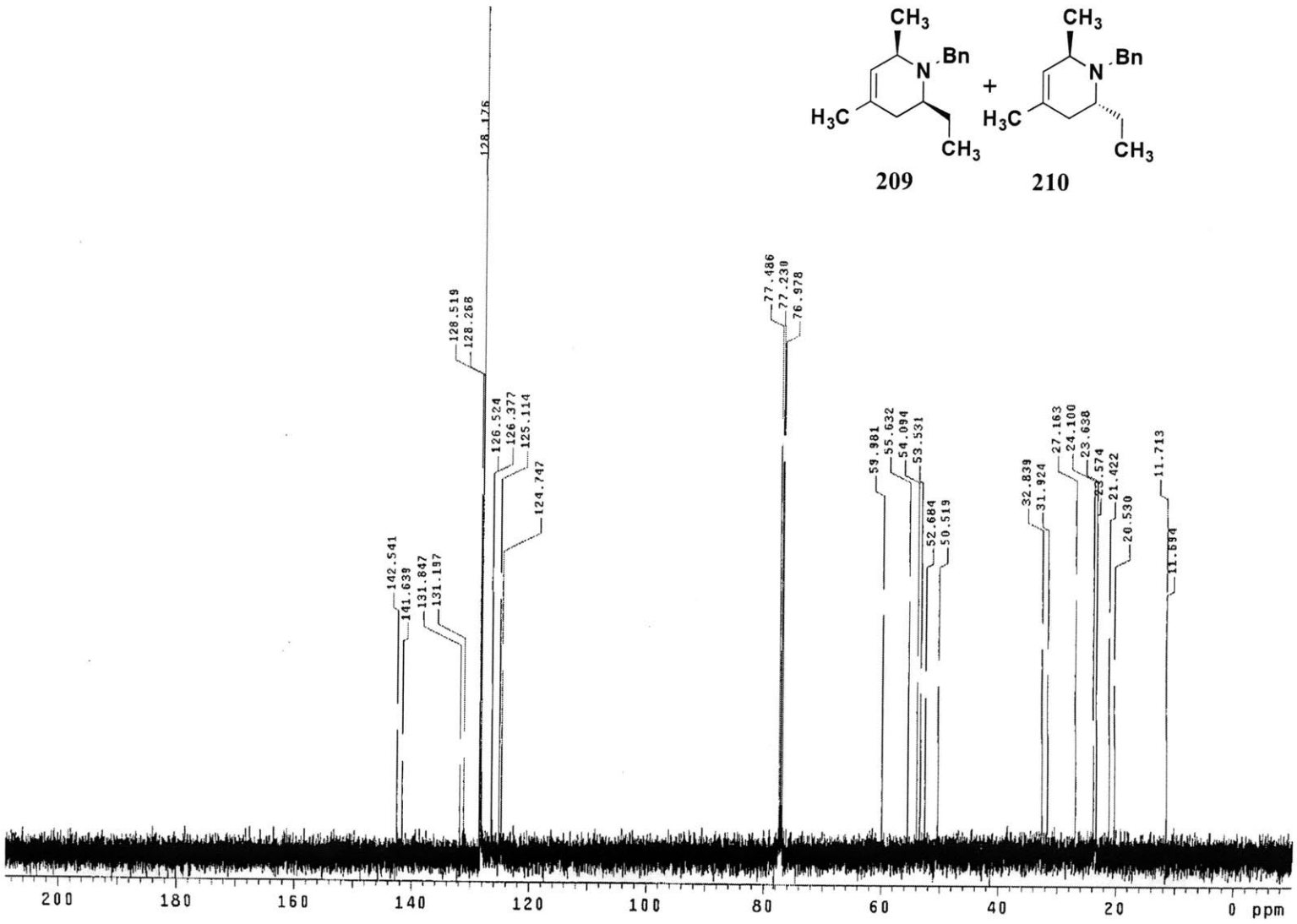
2.76 2.72 ppm
9
8
7
6
5
4
3
2
1
ppm
1.83
1.01
1.90
0.89
2.19
0.98
1.00
0.98
1.13
4.06
1.24
3.01
2.88

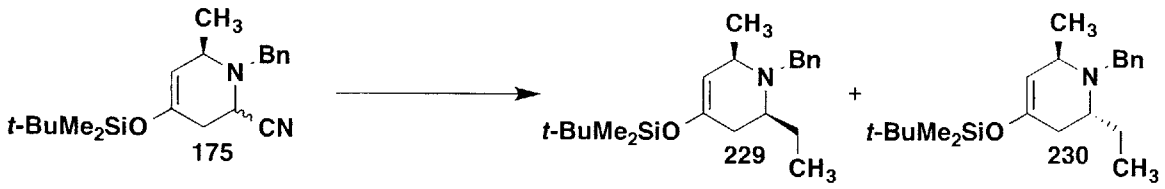
CH3
Bn
N
H3C
CH3

210

142.550
131.225
128.190
126.386
125.118
77.486
77.230
76.978
59.986
55.637
54.071
32.848
27.163
23.578
21.418
11.713
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


CH3
Bn
N
H3C
CH3
+
CH3
Bn
N
H3C
CH3
209
210
3.82 3.76 3.70 ppm
3.3 3.1 2.9 ppm
9 8 7 6 5 4 3 2 1 ppm
2.22 2.24
2.56
1.18
1.09 0.41 0.39 1.00
1.38 1.00 0.42
2.08 0.69 3.68 2.97
1.20 6.23 1.80 1.26


CH3
Bn
N
H3C
CH3
+
209
210
128.176
128.519
128.268
126.524
126.377
125.114
124.747
142.541
141.639
131.847
131.197
77.486
77.230
76.978
59.981
55.632
54.094
53.531
52.684
50.519
32.839
31.924
27.163
24.100
23.638
23.574
21.422
20.530
11.713
11.694
200
180
160
140
120
100
80
60
40
20
0 ppm



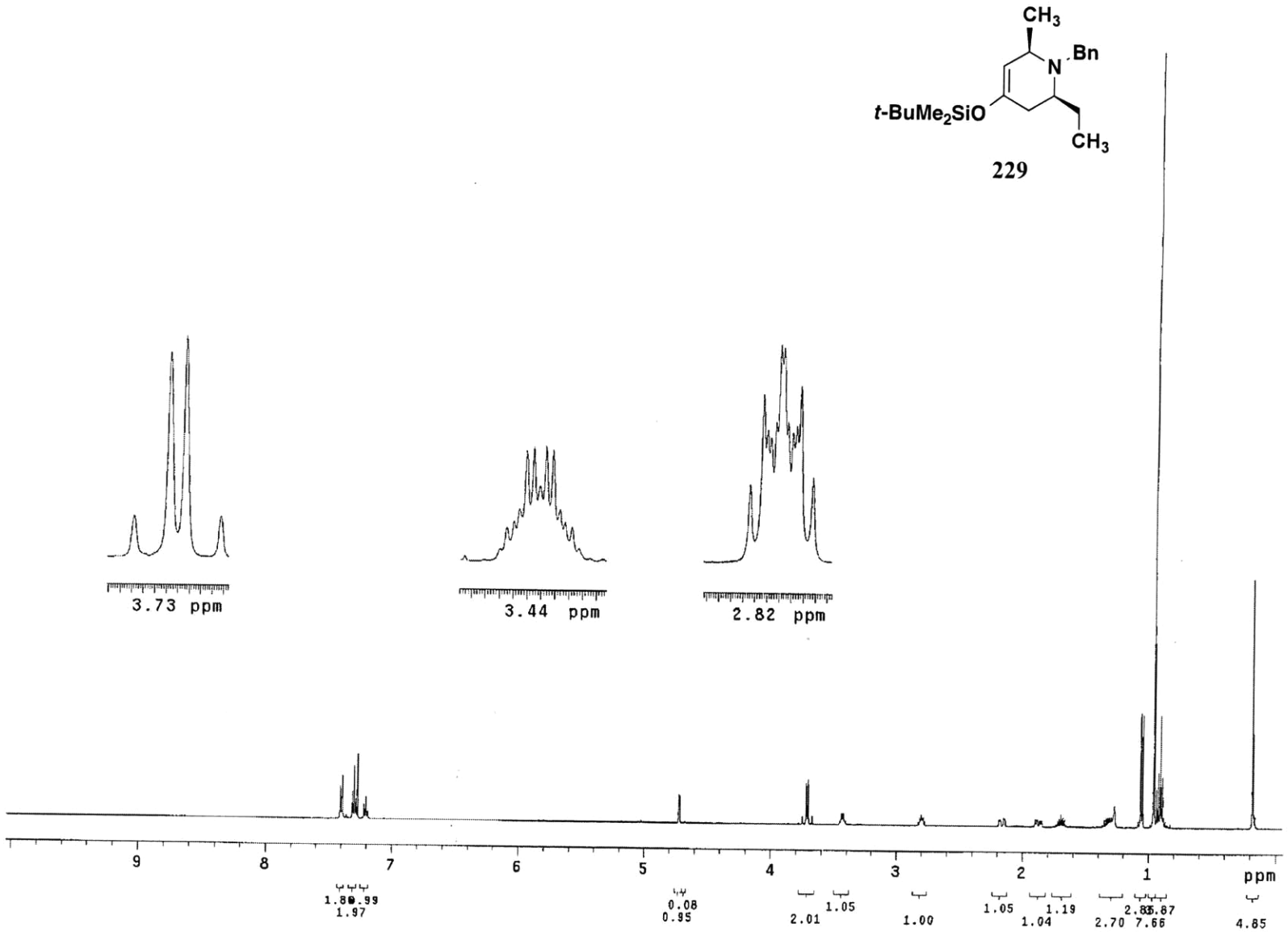
1-Benzyl-2-ethyl-4,6-dimethyl-1,2,3,6-tetrahydropyridine (229 and **230).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **175** (0.113 g, 0.33 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.66 M in Et_2O, 0.25 mL, 0.089 g, 0.66 mmol, 2.0 equiv) was added dropwise via syringe over 2 min. The reaction mixture is allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.106 g of a yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.097 g (85%) of **229** and **230** (54:46 mixture of *cis:trans* isomers based on ^{1}H NMR analysis) as a light yellow oil: IR (thin film) 2959, 2930, 1662, 1463, 1362, 1194, and 837 cm^{-1}; For 2,6-*cis* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.0 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.21 (t, J = 7.5 Hz, 1 H), 4.72 (ddd, J = 2.5, 1.5, 1.3 Hz, 1 H), 3.71 (ABq, J = 15.5 Hz, 2 H), 3.43 (m, 1 H), 2.80 (ddt, J = 8.5, 7.0, 5.5 Hz, 1 H), 2.16 (dddd, J = 17.0, 5.0, 2.7, 1.4 Hz, 1 H), 1.88 (dddd, J = 17.0, 7.0, 2.6, 1.2 Hz, 1 H), 1.70 (m, 1 H), 1.32 (m, 1 H), 1.05 (d, J = 8.0 Hz, 3 H), 0.96 (s, 9 H), 0.91 (t, J = 8.0 Hz, 3 H), 0.18 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 142.6, 128.2, 128.1, 126.4, 107.8, 60.7, 55.0, 53.4, 32.2, 27.5, 26.0, 25.9, 22.0, 18.3, 11.8, -4.1, -4.2; For 2,6-*trans* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.5 Hz, 2 H), 7.31 (t, J = 8.0 Hz, 2 H), 7.23 (t, J = 7.0 Hz, 1 H), 4.76 (d, J = 4.0 Hz, 1 H), 3.73 (d, J = 14.5 Hz, 1 H), 3.39 (d, J = 14.5 Hz, 1 H), 3.16 (m, 1 H), 2.95 (m, 1H), 1.93 (m, 1 H), 1.63 (m, 1 H), 1.50 (m, 1 H), 1.09 (d, J = 7.0 Hz, 1 H), 0.99 (t, J = 7.5 Hz, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (125

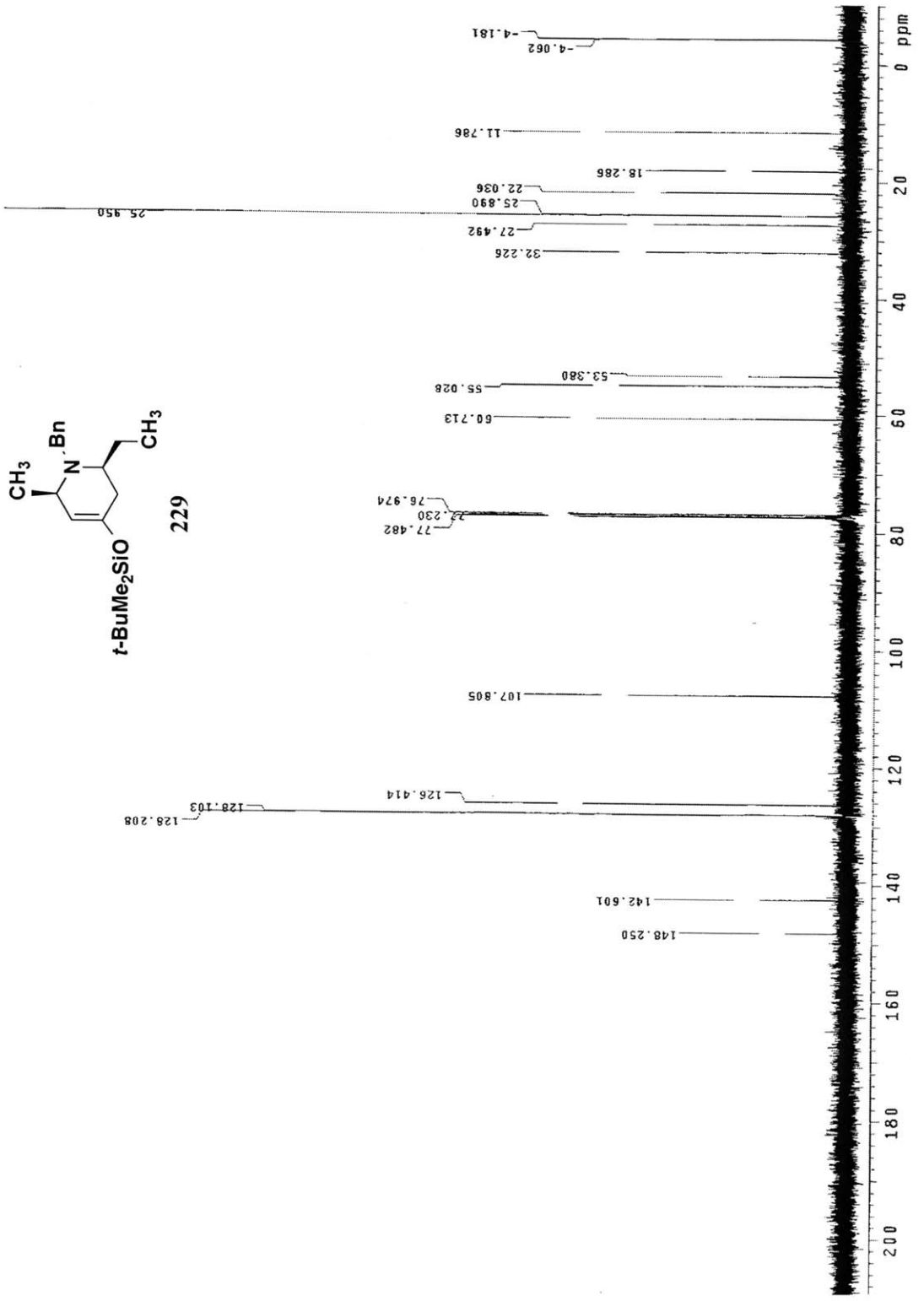
MHz, $CDCl_3$) δ 148.5, 141.5, 128.5, 128.3, 126.6, 107.7, 53.8, 51.9, 50.1, 31.9, 26.0, 24.8, 21.3, 18.3, 11.6, -4.1, -4.3; HRMS (m/z) [M-H] calcd for $C_{21}H_{35}NOSi$: 344.2404. Found: 344.2410.

1-Benzyl-2-ethyl-4,6-dimethyl-1,2,3,6-tetrahydropyridine (229 and **230).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.093 mL, 0.067 g, 0.66 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.70 M in hexanes, 0.24 mL, 0.66 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **175** (0.113 g, 0.330 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.110 mL, 0.207 g, 1.32 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.122 g of yellow oil that was used immediately in the next step without further purification.

Approximately 20 mL of NH_3 was condensed at -78 °C into a 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and a Dewar condenser fitted with a rubber septum and argon inlet needle. Sodium metal (0.076 g, 3.3 mmol, 10.0 equiv) was added and the resulting blue solution was stirred at -78 °C for 30 min. A solution of the amino nitrile prepared above in 3 mL of THF was then added, and the resulting mixture was stirred at -78 °C for 5 min. Satd NH_4Cl solution (10 mL) was added dropwise via syringe over 5 min. The rubber septum was removed from the Dewar condenser and allowed to warm to rt over 3 h while the NH_3 evaporated. The resulting mixture was poured into 30 mL of satd $NaHCO_3$ solution and extracted with three 20-mL portions of ether. The combined organic layers were washed with 30 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.112 g of yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution hexanes containing 1% Et_3N)

afforded 0.088 g (77%) of **229** and **230** (62:38 ratio based on ^{1}H NMR analysis) as a light yellow oil with spectral data identical with that reported previously.


CH3
Bn
N
t-BuMe2SiO
CH3
229
3.73 ppm
3.44 ppm
2.82 ppm
9
8
7
6
5
4
3
2
1
ppm
1.97
0.95
2.01
1.00
1.04
4.85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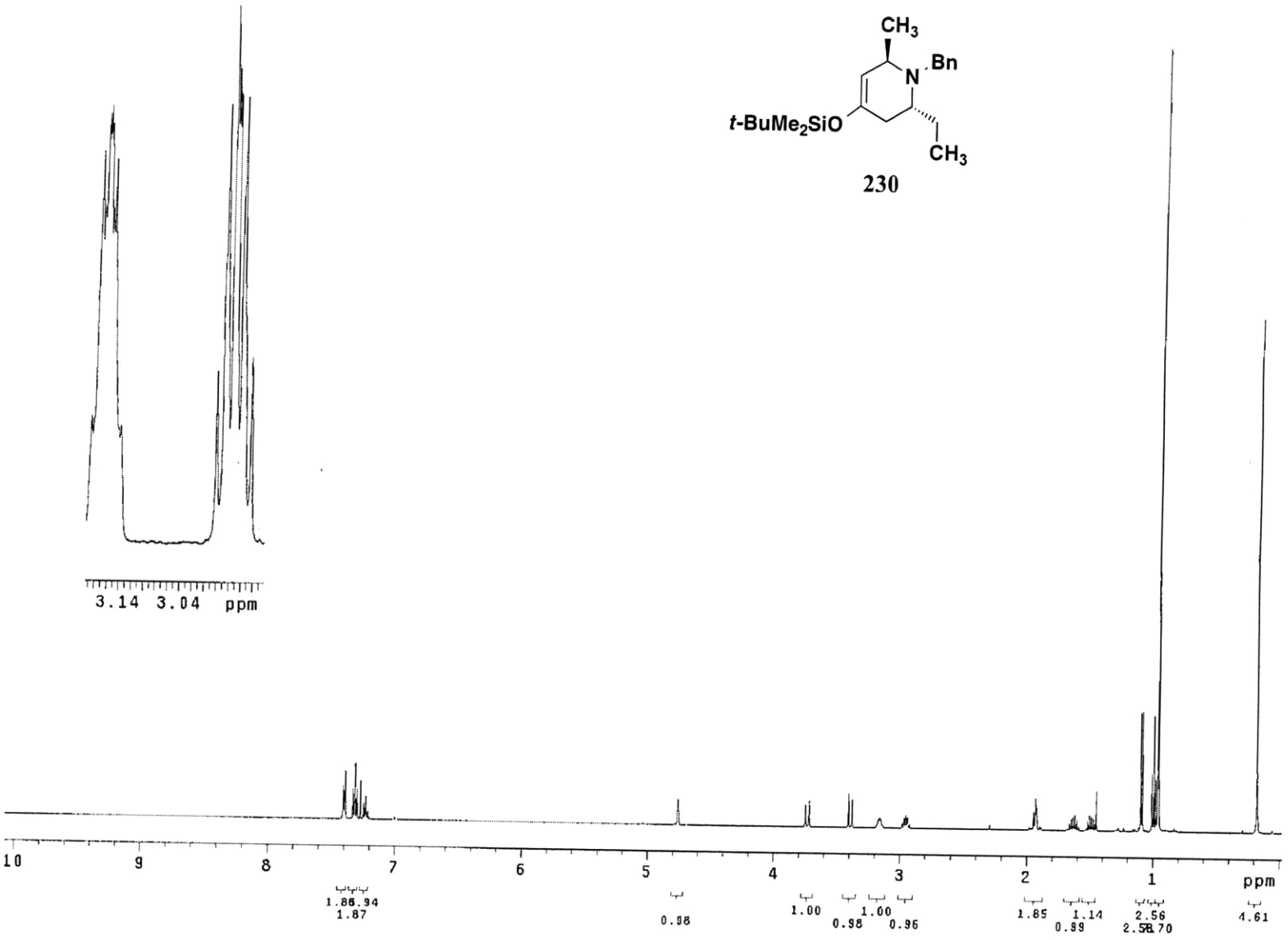
-4.062
11.786
18.286
22.036
25.890
25.950
27.492
32.226
53.380
55.028
60.713
76.974
77.230
77.482
107.805
126.414
128.103
128.208
142.601
148.250
ppm
0
20
40
60
80
100
120
140
160
180
200
CH3
N
Bn
CH3
t-BuMe2SiO
229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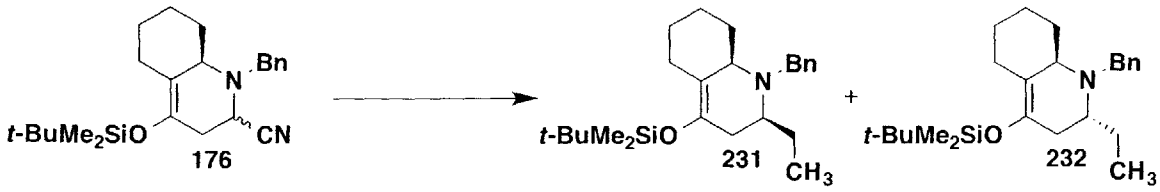
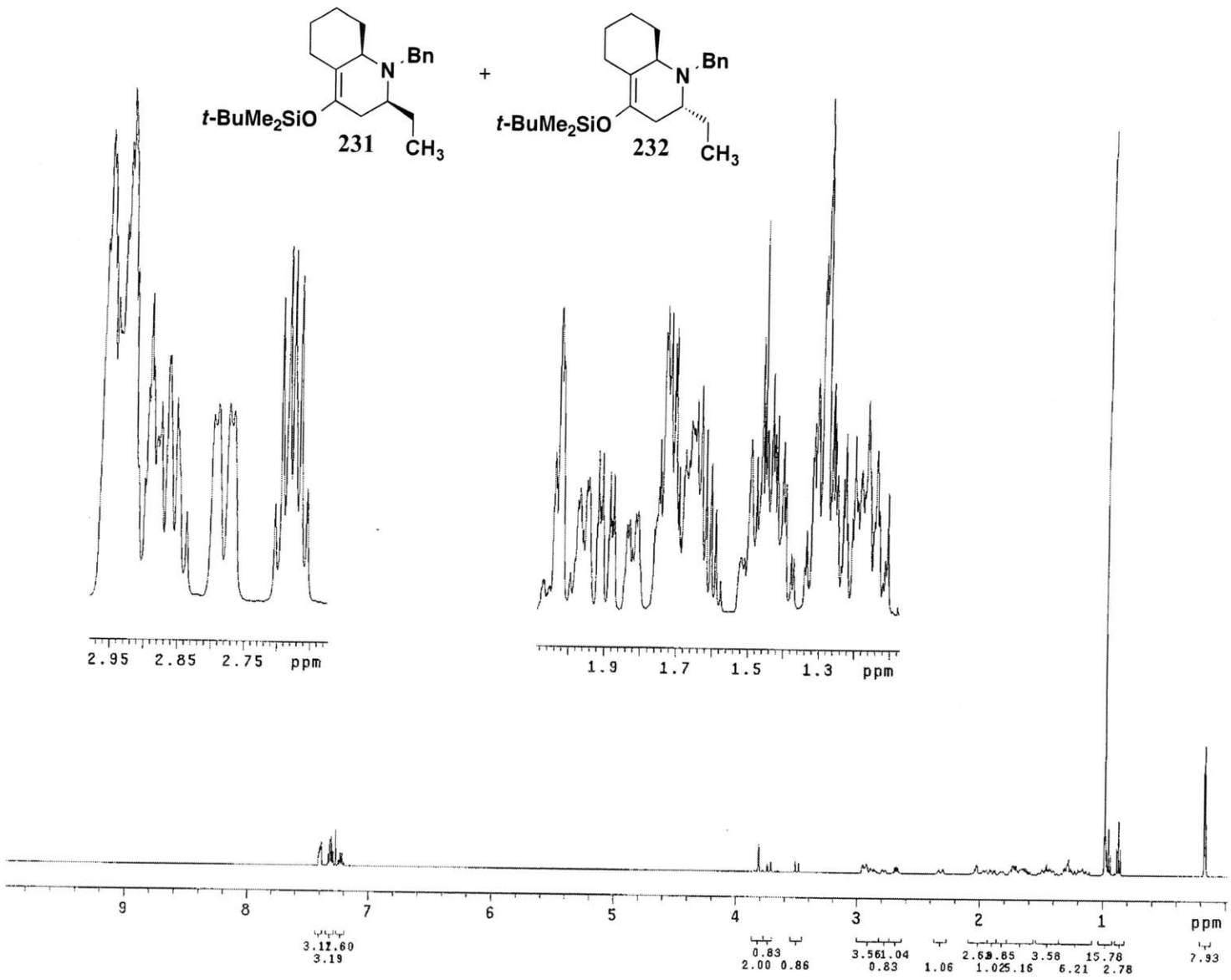
Bn
N
t-BuMe2SiO
CH3
230
3.14 3.04 ppm
10
9
8
7
6
5
4
3
2
1
ppm
1.86 0.94
1.87
0.98
1.00
0.98
1.00
0.96
1.85
0.99
1.14
2.56
2.58 1.70
4.61

CH3
Bn
N
t-BuMe2SiO
CH3
230
148.529
141.534
128.455
128.313
126.592
107.700
77.482
77.230
76.974
53.810
51.892
50.047
31.873
25.954
24.801
21.271
18.291
11.644
-4.062
-4.264
200
180
160
140
120
100
80
60
40
20
0
ppm



1-Benzyl-4-(tert-butyldimethylsiloxy)-2-ethyl-1,2,3,5,6,7,8,8a-octahydroquinoline (231 and **232).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **176** (0.098 g, 0.25 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.66 M in Et_2O, 0.19 mL, 0.068 g, 0.51 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The reaction mixture is allowed to warm to rt over 3.5 h and then diluted with 10 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.099 g of a yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.081 g (84%) of **231** and **232** (57:43 mixture of *cis:trans* isomers based on ^{1}H NMR analysis) as a light yellow oil: IR (thin film) 2929, 2856, 1688, 1462, 1255, 1194, and 837 cm^{-1}; For 2,6-*cis* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.0 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.21 (t, J = 7.5 Hz, 1 H), 3.80 (br s, 2 H), 2.89-2.95 (m, 2 H), 2.64-2.95 (m, 1 H), 2.30 (dm, J = 17.5 Hz, 1 H), 1.95 (dm, J = 12.5 Hz, 1 H), 1.88 (dm, J = 16.0 Hz, 1 H), 1.62-1.74 (m, 3 H), 1.48 (br t, J = 13.0 Hz, 1 H), 1.10-1.33 (m, 4 H), 0.97 (s, 9 H), 0.86 (t, J = 7.5 Hz, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 138.5, 128.2, 128.2, 126.5, 116.3, 116.3, 62.2, 59.7, 57.2, 34.8, 33.3, 27.3, 26.9, 26.3, 26.1, 26.1, 18.4, 11.8, -3.5, -3.8; For 2,6-*trans* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 2 H), 7.31 (m, 2 H), 7.23 (m, 1 H), 3.73 (d, J = 14.0 Hz, 1 H), 3.50 (d, J = 14.0 Hz, 1 H), 2.84-2.93 (m, 1 H), 2.78 (br d, J = 11.5 Hz, 1 H), 1.96-2.07 (m, 2 H), 1.83 (m, 1 H), 1.58-1.69 (m, 3 H), 1.36-1.52 (m, 3 H), 1.12-1.34 (m, 3 H), 0.97 (s, 9 H), 0.95 (t, J = 7.5 Hz, 3 H), 0.17 (s, 3 H), 0.16

(s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 139.1, 128.4, 128.3, 126.5, 117.2, 60.3, 55.7, 50.8, 34.0, 32.6, 26.7, 26.1, 23.7, 18.4, 11.8, -3.7, -3.8; HRMS (m/z) [M-H] calcd for $C_{24}H_{39}NOSi$: 384.2730. Found: 384.2730.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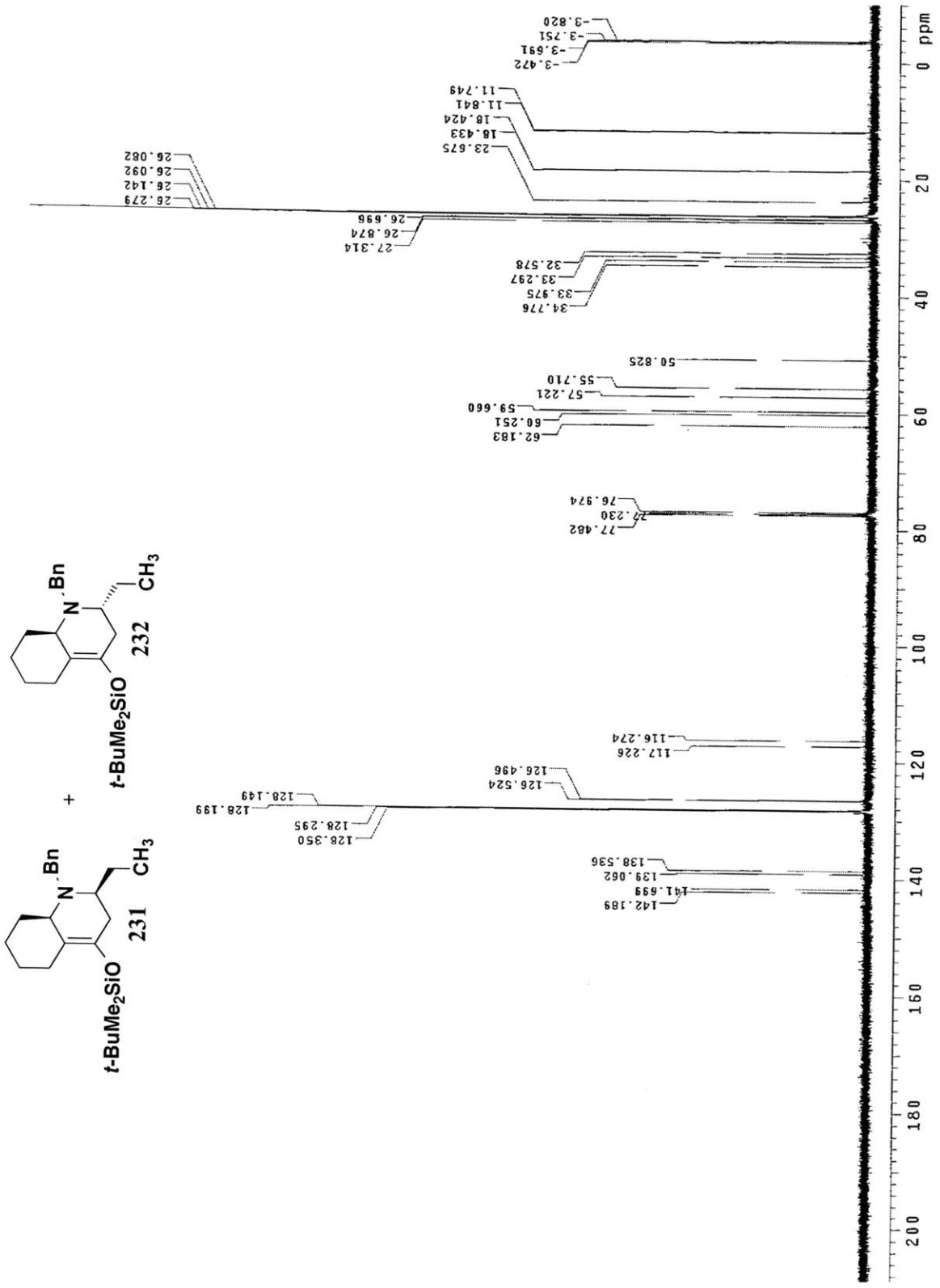
N
Bn
CH3
231
+
t-BuMe2SiO
N
Bn
CH3
232
2.95 2.85 2.75 ppm
1.9 1.7 1.5 1.3 ppm
9 8 7 6 5 4 3 2 1 ppm
3.11 1.60
3.19
0.83
2.00 0.86
3.56 1.04
0.83
1.06
2.63 3.85 3.58 15.78
1.02 5.16 6.21 2.78
7.93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-3.751
-3.691
-3.472
11.749
11.841
18.424
18.433
23.675
26.082
26.092
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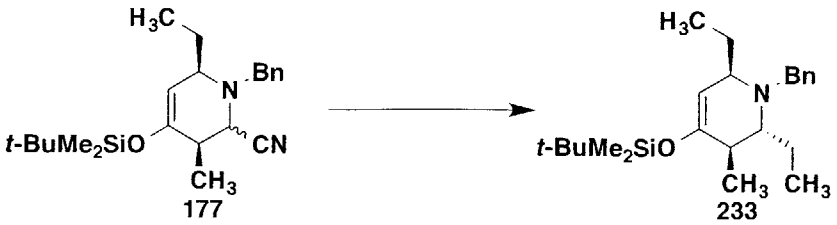
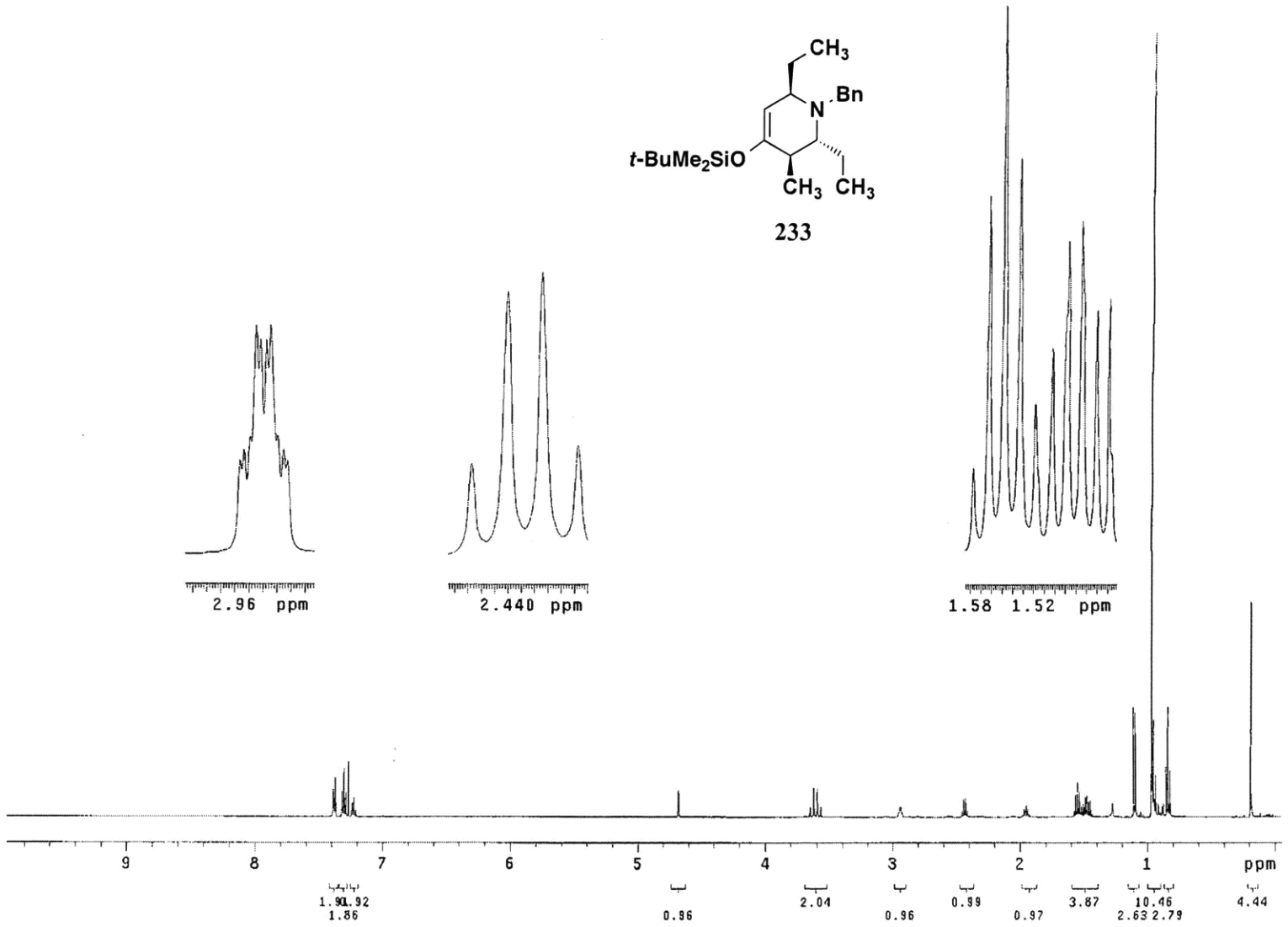
26.279
26.696
26.874
27.314
32.578
33.297
33.975
34.776
50.825
55.710
57.221
59.660
60.251
62.183
76.974
77.230
77.482
116.274
117.226
126.496
126.524
128.149
128.199
128.295
128.350
138.536
139.062
141.699
142.189
0 ppm
20
40
60
80
100
120
140
160
180
200
N
Bn
CH3
232
t-BuMe2SiO
+
N
Bn
CH3
231
t-BuMe2SiO



1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2,6-diethyl-3-methyl-1,2,3,6-tetrahydropyridine (233). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **177** (0.127 g, 0.342 mmol, 1.0 equiv) in 4 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.73 M in Et_2O, 0.25 mL, 0.091 g, 0.68 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The reaction mixture was allowed to warm to rt over 3.5 h and then diluted with 15 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.118 g of a light yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.112 g (88%) of **233** as a colorless oil: IR (thin film) 2959, 2930, 2858, 1657, 1463, 1253, 1199, and 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.0 Hz, 2 H), 7.23 (t, J = 7.0 Hz, 1 H), 4.68 (d, J = 3.6 Hz, 1 H), 3.61 (AB q, J = 14.0 Hz, 2 H), 2.94 (m, 1 H), 2.43 (q, J = 6.5 Hz, 1 H), 1.95 (m, 1 H), 1.55 (m, 2 H), 1.48 (m, 2 H), 1.10 (d, J = 7.0 Hz, 3 H), 0.96 (s, 9 H), 0.95 (t, J = 7.5 Hz, 3 H), 0.84 (t, J = 7.5 Hz, 3 H), 0.19 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 141.4, 128.8, 128.2, 126.6, 105.4, 61.1, 56.7, 51.0, 36.3, 27.2, 26.1, 19.8, 18.3, 16.7, 12.0, 10.1, -4.1, -4.2; HRMS (m/z) [M-H] calcd for $C_{23}H_{39}NOSi$: 374.2874. Found: 374.2881.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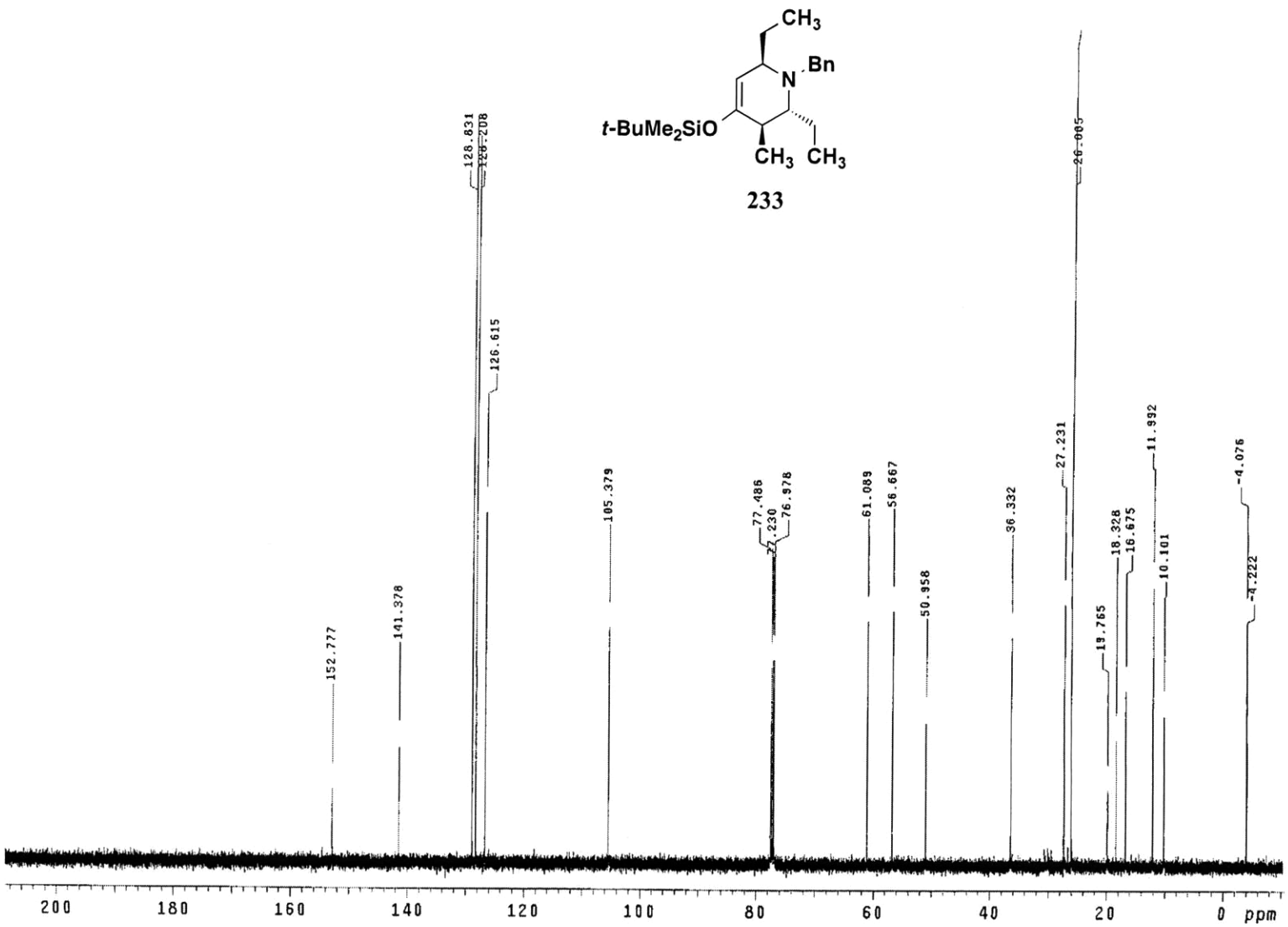
Bn
N
t-BuMe2SiO
CH3 CH3
233
2.96 ppm
2.440 ppm
1.58 1.52 ppm
9
8
7
6
5
4
3
2
1
ppm
1.90 1.92
1.86
0.96
2.04
0.96
0.99
0.97
3.87
10.46
2.63 2.79
4.44


CH3
N
Bn
t-BuMe2SiO
CH3 CH3
233
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128.208
126.615
105.379
77.486
77.230
76.978
61.089
56.667
50.958
36.332
27.231
20.005
18.765
18.328
16.675
11.992
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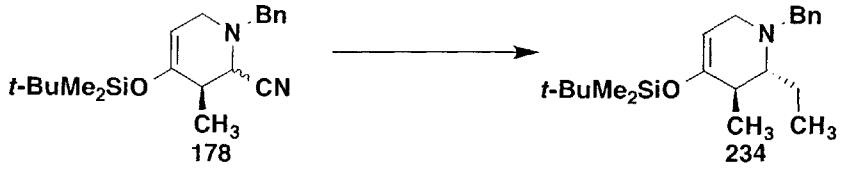
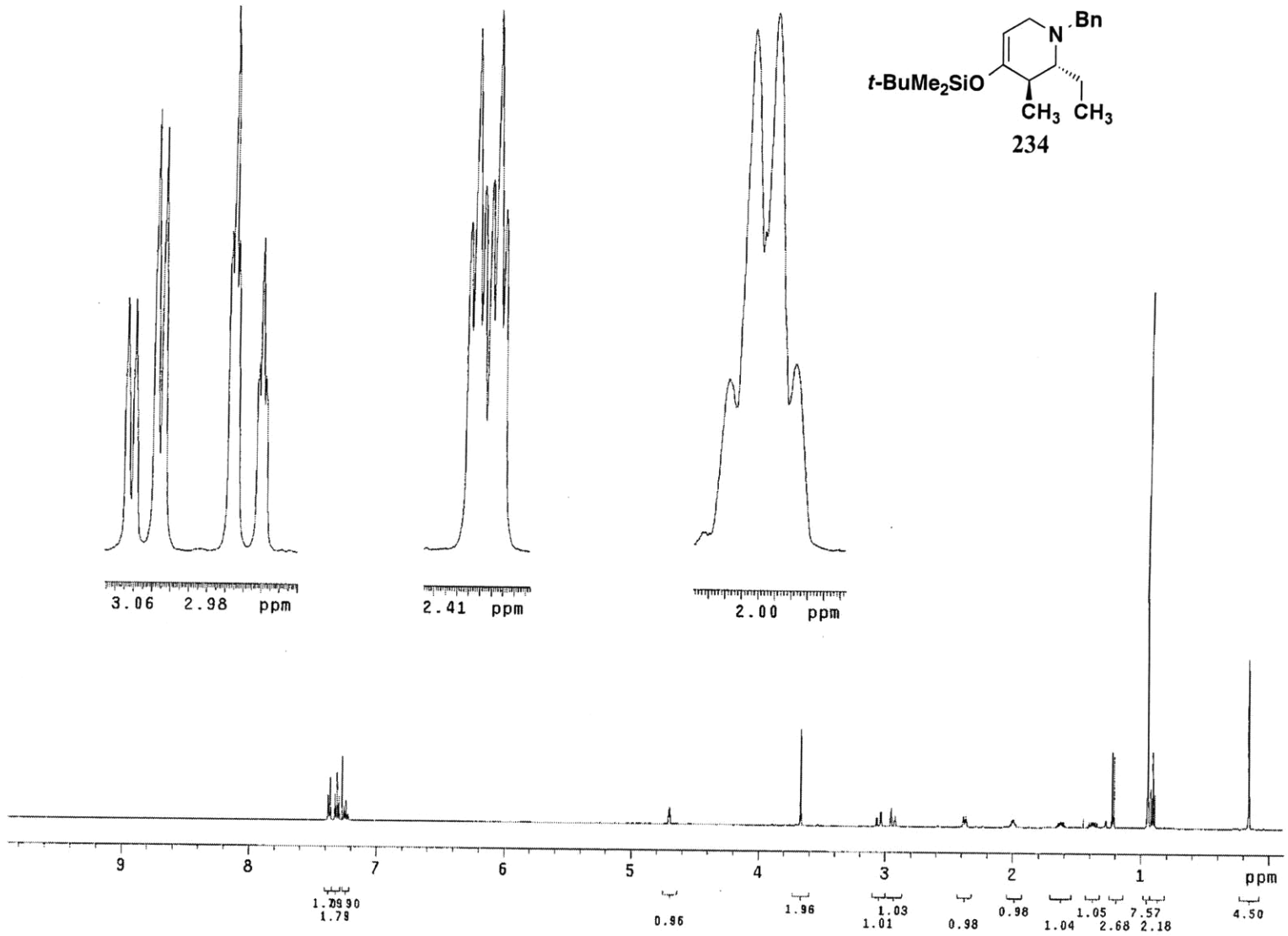
-4.222
200
180
160
140
120
100
80
60
40
20
0 ppm



1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-ethyl-3-methyl-1,2,5,6-tetrahydropyridine (234). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of amino nitrile **178** (0.150 g, 0.438 mmol, 1.0 equiv) in 5 mL of Et_2O. The reaction mixture was cooled at -30 °C and ethylmagnesium bromide (2.72 M in Et_2O, 0.322 mL, 0.117 g, 0.876 mmol, 2.0 equiv) was added dropwise via syringe over 2 min. The reaction mixture was allowed to warm to rt over 3.5 h and then diluted with 15 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.154 g of a light yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.133 g (88%) of **234** as a colorless oil: IR (thin film) 2959, 2930, 2858, 1675, 1461, 1199, and 867 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.0 Hz, 2 H), 7.31 (t, J = 7.0 Hz, 2 H), 7.24 (t, J = 7.0 Hz, 1 H), 4.70 (dd, J = 4.4, 2.5 Hz, 1 H), 3.67 (s, 2 H), 3.05 (dd, J = 15.5, 4.2 Hz, 1 H), 2.94 (dt, J = 16.0, 1.7 Hz, 1 H), 2.37 (dt, J = 9.0, 3.2 Hz, 1 H), 2.00 (m, 1 H), 1.62 (m, 1 H), 1.38 (m, 1 H), 1.22 (d, J = 7.5 Hz, 3 H), 0.95 (s, 9 H), 0.91 (t, J = 7.5 Hz, 3 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 140.4, 128.8, 128.3, 126.9, 100.3, 65.0, 57.6, 46.9, 37.9, 25.9, 18.6, 18.2, 17.5, 11.8, -4.2, -4.2; HRMS (m/z) [M-H] calcd for $C_{21}H_{35}NOSi$: 344.2404. Found: 344.2415.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CH3
CH3
234
3.06
2.98
ppm
2.41
ppm
2.00
ppm
9
8
7
6
5
4
3
2
1
ppm
1.79
0.96
1.96
1.03
1.01
0.98
0.98
1.05
1.04
7.57
2.68
2.18
4.50

Bn
N
t-BuMe2SiO
CH3
CH3
234
152.621
140.362
128.817
128.318
126.890
100.334
77.482
77.230
76.974
65.007
57.623
46.884
37.902
25.931
18.570
18.232
17.499
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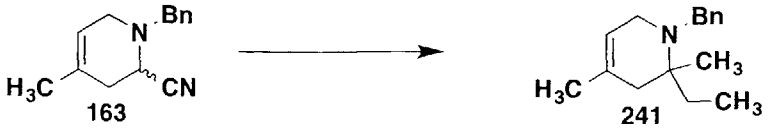
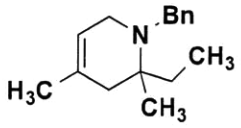
140
120
100
80
60
40
20
0
ppm



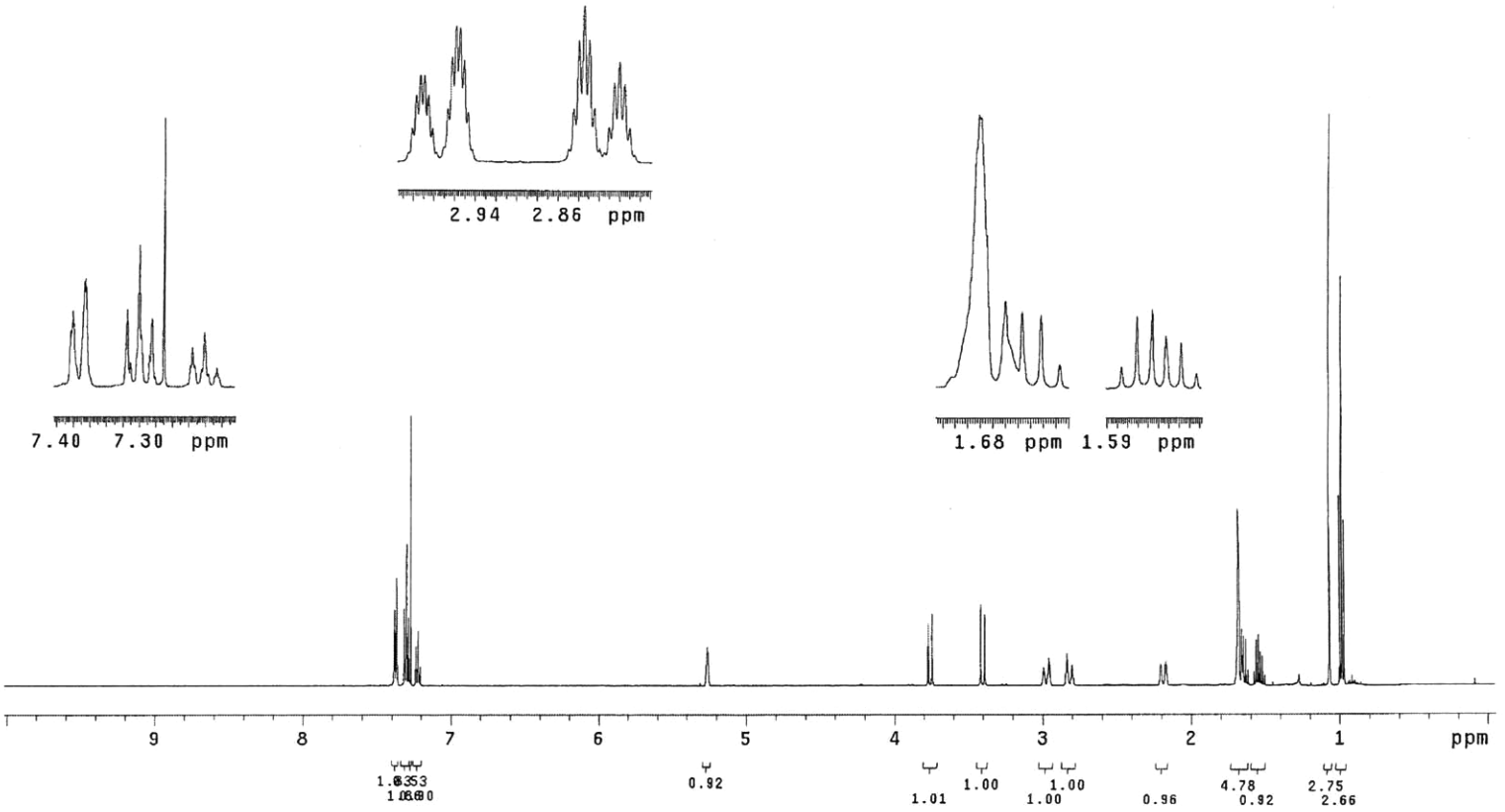
1-Benzyl-2-ethyl-2,4-dimethyl-1,2,3,6-tetrahydropyridine (241). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.259 mL, 0.190 g, 1.88 mmol, 2.0 equiv) in 4 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.44 M in hexanes, 0.770 mL, 1.88 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **163** (0.200 g, 0.940 mmol, 1.0 equiv) in 3 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.313 mL, 0.592 g, 3.77 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 mL of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.227 g of an orange oil that was used immediately in the next step without further purification.

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with $CeCl_3$ (0.694 g, 2.82 mmol, 3.0 equiv) and 7 mL of THF and the solution was stirred at rt for 2 h. The resulting mixture was cooled at -78 °C while methylmagnesium bromide (2.81 M solution in Et_2O, 1.00 mL, 2.82 mmol. 3.0 equiv) was added dropwise over 2 min. The solution of the amino nitrile prepared above in 2 mL of THF was then added dropwise over 2 min. The reaction mixture was allowed to warm to rt over 3 h, stirred at room temperature for 16 h, and then diluted with 15 mL of satd aq NH_4Cl solution. The aqueous layer was extracted with three 15-mL portions of Et_2O, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.210 g of an orange oil. Purification by column chromatography on

15 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1 % Et_3N) afforded 0.114 g (53%) of **241** as a light yellow oil: IR (thin film) 2965, 2923, 1453, 1370, 1139, and 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.0 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.22 (t, J = 7.5 Hz, 1 H), 5.26 (br s, 1 H), 3.76 (d, J = 13.0 Hz, 1 H), 3.40 (d, J = 13.0 Hz, 1 H), 2.97 (dm, J = 17.5 Hz, 1 H), 2.81 (dm, J = 17.0 Hz, 1 H), 2.18 (d, J = 17.0 Hz, 1 H), 1.68 (d, J = 17.0 Hz, 1 H), 1.68 (s, 3 H), 1.61-1.70 (m, 1 H), 1.49-1.58 (m, 1 H), 1.06 (s, 3 H), 0.98 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 131.5, 128.9, 128.4, 126.7, 118.5, 54.7, 53.1, 48.1, 40.5, 30.5, 23.5, 19.9, 8.2; HRMS (m/z) $[M+H]^+$ calcd for $C_{16}H_{23}N$: 230.1903. Found: 230.1903.


Bn
N
CH3
H3C
CH3

241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1.68 ppm 1.59 ppm
9 8 7 6 5 4 3 2 1 ppm
0.92
1.01
1.00
1.00
1.00
0.96
4.78
0.92
2.75
2.66

Bn
N
CH3
H3C
CH3
241
128.858
126.711
118.508
77.482
77.230
76.974
54.620
53.110
48.074
40.539
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23.542
19.898
8.100
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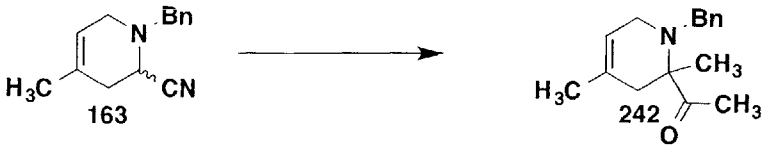
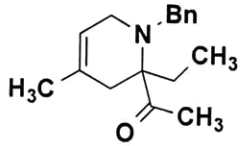
140
120
100
80
60
40
20
0 ppm



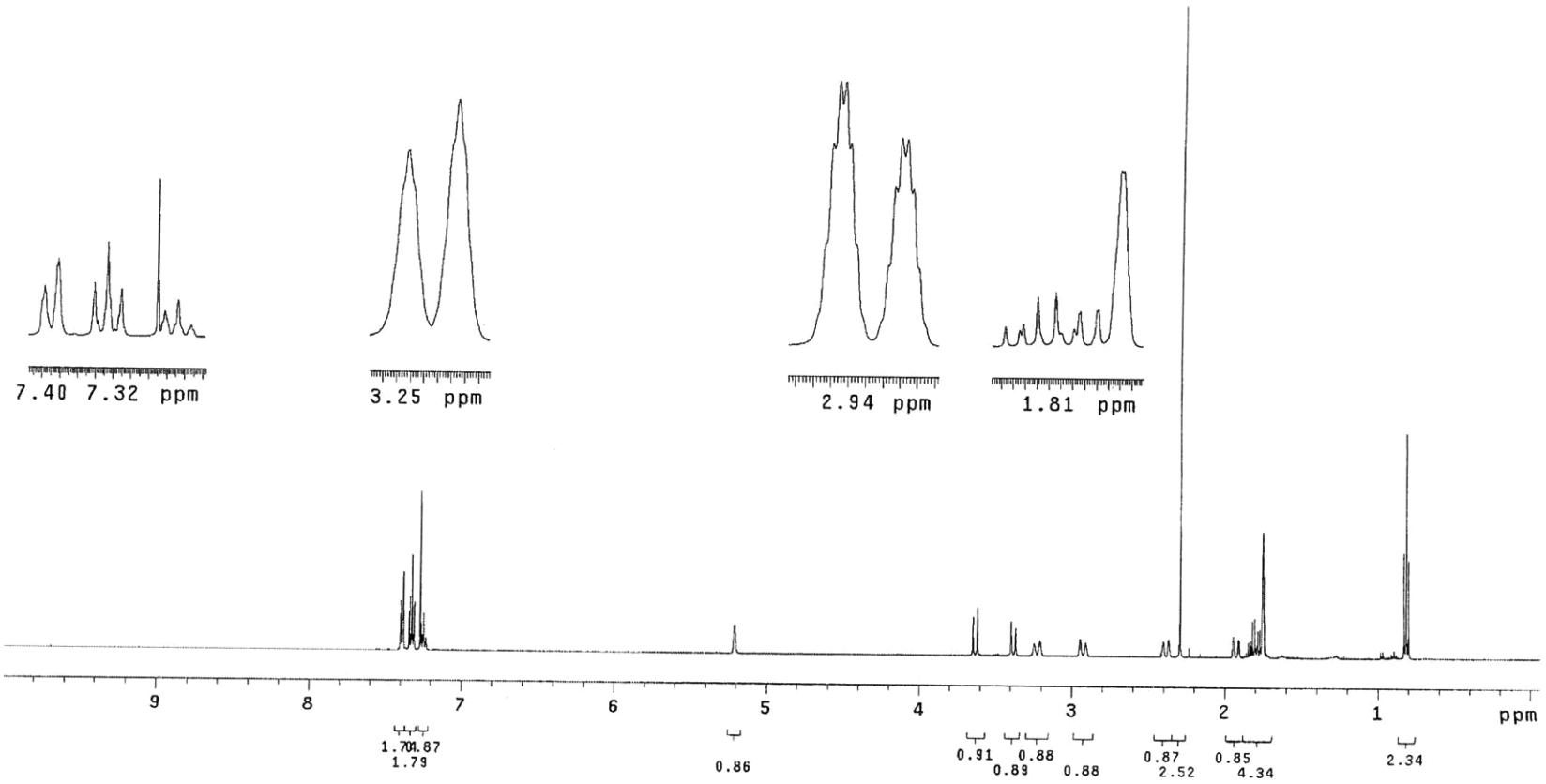
1-(1-Benzyl-2-ethyl-1,2,3,6-tetrahydro-4-methyl-2-pyridinyl)ethanone (242). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.179 mL, 0.131 g, 1.29 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.44 M in hexanes, 0.528 mL, 1.29 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **163** (0.137 g, 0.645 mmol, 1.0 equiv) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.214 mL, 0.405 g, 2.58 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 12 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.156 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the amino nitrile prepared above in 4 mL of Et_2O. The solution was cooled at -78 °C while MeLi solution (0.97 M in ether, 2.01 mL, 1.95 mmol, 3.0 equiv) was added dropwise via syringe over 1 min. The reaction mixture was allowed to warm to rt over 3.5 h and then diluted with 12 mL of satd aq NH_4Cl solution. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.176 g of a yellow oil. This material was dissolved in 5 mL of Et_2O and the flask was fitted with an argon inlet adapter and purged with argon. Silica gel (3.0 g) was added and the resulting slurry was stirred at rt for 16 h. The mixture was then filtered with the aid of 20 ml of ether and concentrated to afford 0.182 g of yellow oil. Column

chromatography on 12 g of Et_3N-deactivated silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) provided 0.123 g (74%) of **242** as a yellow oil: IR (thin film) 3027, 2969, 2929, 1711, 1604, 1452, 1350, 1124, and 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.0 Hz, 2 H), 7.33 (t, J = 7.5 Hz, 2 H), 7.25 (t, J = 7.0 Hz, 1 H), 5.21 (br s, 1 H), 3.63 (d, J = 14.0 Hz, 1 H), 3.37 (d, J = 14.5 Hz, 1 H), 3.22 (br d, J = 18.5 Hz, 1 H), 2.93 (br d, J =18.0 Hz, 1 H), 2.49 (br d, J = 17.5 Hz, 1H), 2.29 (s, 3 H), 1.93 (br d, J = 18.0 Hz, 1 H), 1.75 (s, 3 H), 1.76-1.87 (m, 2 H), 0.82 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 140.0, 131.8, 128.5, 128.3, 127.0, 117.3, 70.3, 54.2, 46.3, 29.4, 27.7, 25.0, 23.7, 8.8; HRMS (m/z) $[M+H]^+$ calcd for $C_{17}H_{23}NO$: 258.1852. Found: 258.1851.


Bn
N
CH3
H3C
CH3
O

242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2.94 ppm
1.81 ppm
9
8
7
6
5
4
3
2
1
ppm
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0.91
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0.89
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0.87
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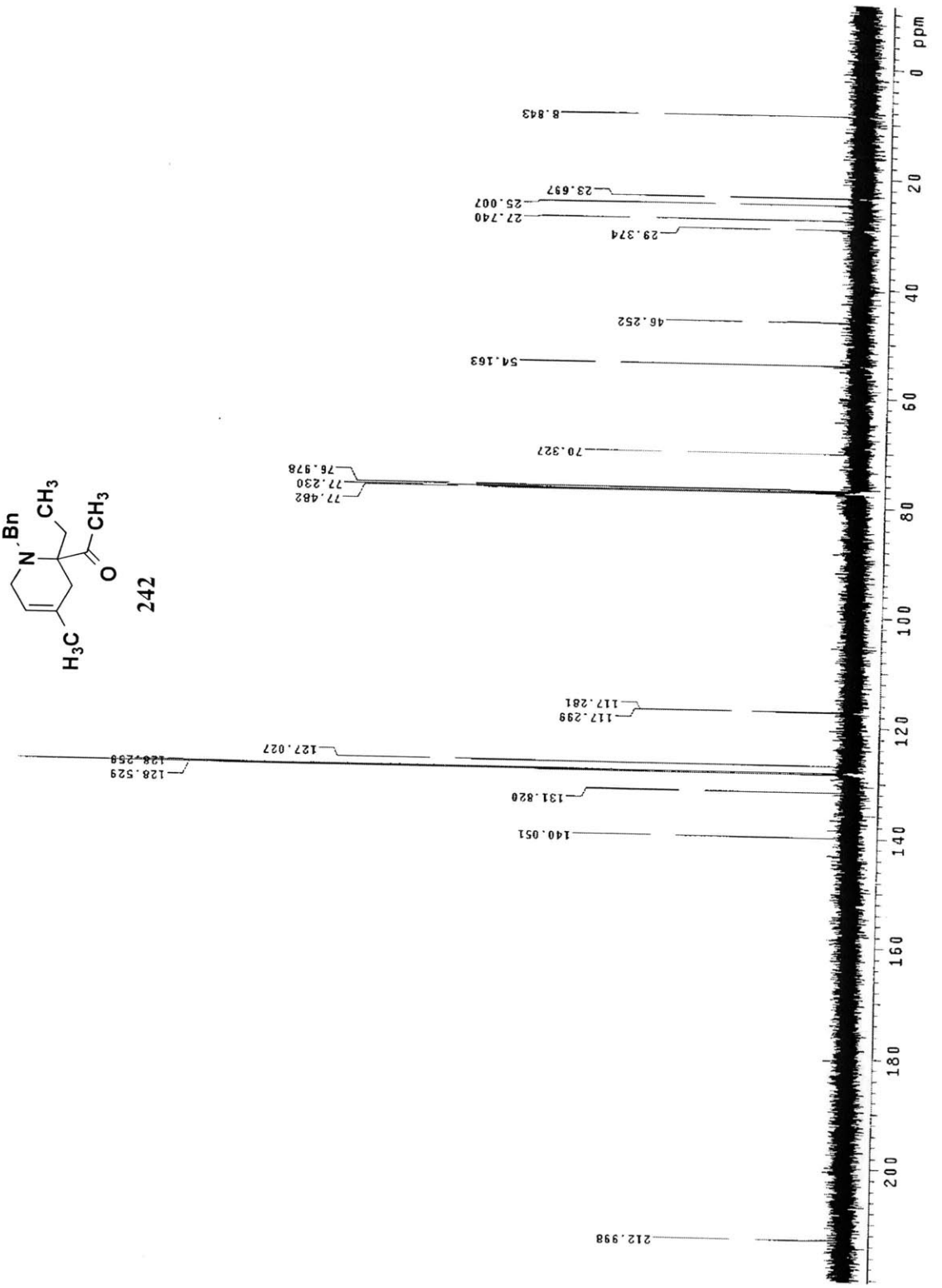
0.85
4.34
2.34


242
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25.007
27.740
29.374
46.252
54.163
70.327
76.978
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77.482
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128.529
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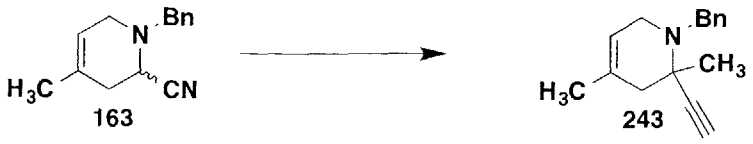
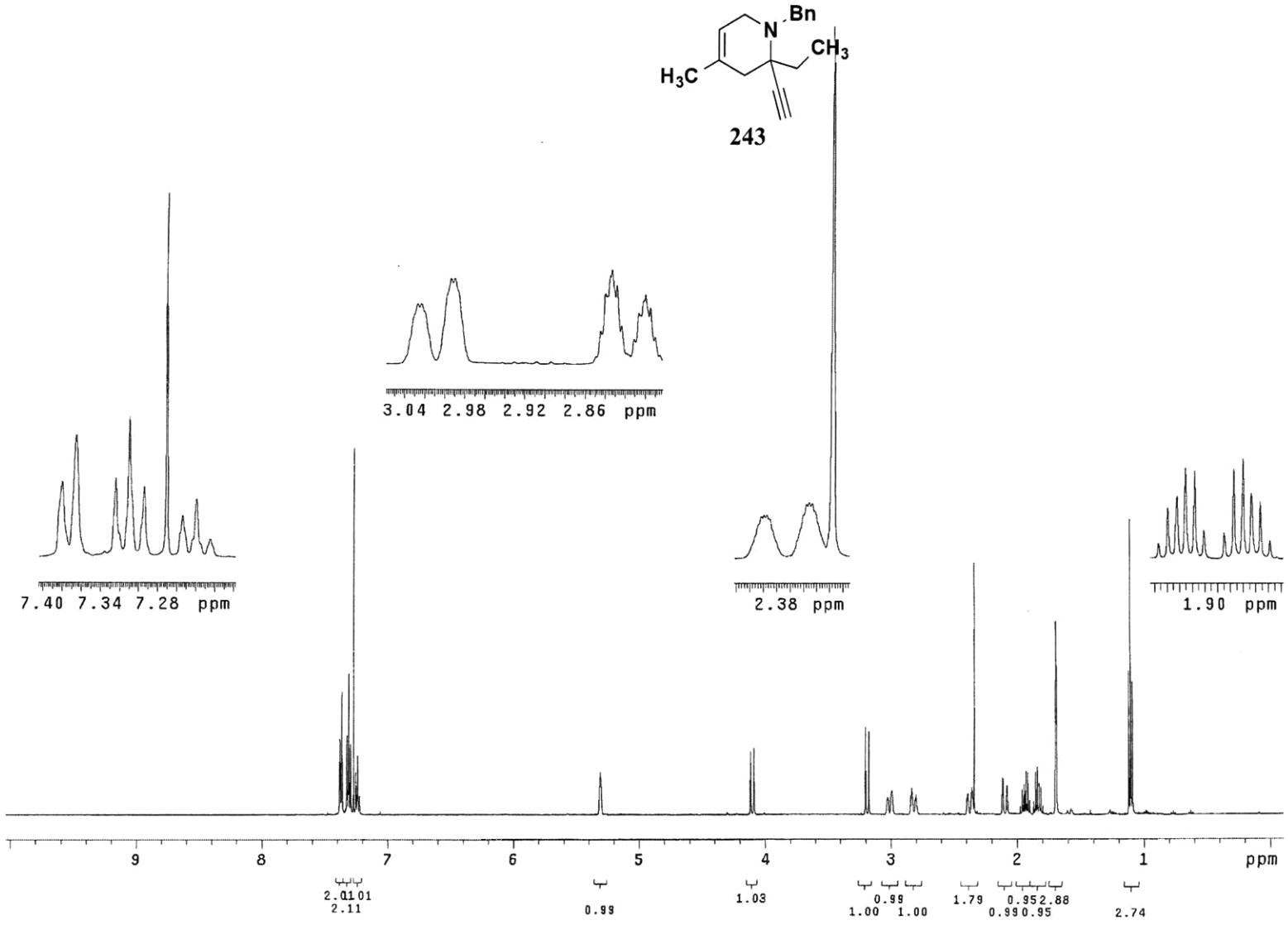
140.051
212.998
0 ppm



1-Benzyl-2-ethyl-2-ethynyl-3-methyl-1,2,3,6-tetrahydropyridine (243). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.155 mL, 0.114 g, 1.13 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.44 M in hexanes, 0.463 mL, 1.13 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **163** (0.120 g, 0.565 mmol, 1.0 equiv) in 1.5 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.188 mL, 0.356 g, 2.28 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 12 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.136 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the amino nitrile prepared above in 4 mL of Et_2O. The solution was cooled at -78 °C while ethynylmagnesium bromide solution (0.50 M in THF, 3.42 mL, 1.71 mmol, 3.0 equiv) was added dropwise via syringe over 3 min. The reaction mixture was allowed to warm to rt over 3 h, stirred at rt for 16 h, and then diluted with 12 mL of satd aq NH_4Cl solution. The aqueous layer was extracted with three 15-mL portions of ether, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.126 g of an orange oil. Column chromatography on 15 g of Et_3N-deactivated silica gel (elution with hexanes containing 1% Et_3N) afforded 0.106 g (74%) of **243** as a yellow oil: IR (thin film) 3298, 3028, 2970, 2929, 1495, 1452, 1362, 1158, and 632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.0 Hz, 2 H),

7.31 (t, J = 7.0 Hz, 2 H), 7.24 (t, J = 7.0 Hz, 1 H), 5.31 (d, J = 2.0 Hz, 1 H), 4.10 (d, J = 13.0 Hz, 1 H), 3.19 (d, J = 13.0 Hz, 1 H), 3.01 (dm, J = 17.0 Hz, 1 H), 2.82 (dm, J = 17.0 Hz, 1 H), 2.37 (d, J = 18.0 Hz, 1 H), 2.34 (s, 1 H), 2.10 (d, J = 18.0 Hz, 1 H), 1.94 (dq, J = 14.5, 7.5 Hz, 1 H), 1.84 (dq, J = 14.5, 7.5 Hz, 1 H), 1.69 (s, 3 H), 1.10 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 130.2, 129.1, 128.5, 127.0, 119.0, 84.5, 71.8, 56.6, 54.7, 49.2, 40.8, 32.1, 23.2, 8.2; HRMS (m/z) $[M+H]^+$ calcd for $C_{17}H_{21}N$: 240.1747. Found: 240.1754.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H3C
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2.38 ppm
1.90 ppm
9
8
7
6
5
4
3
2
1
ppm
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1.03
0.99
1.00 1.00
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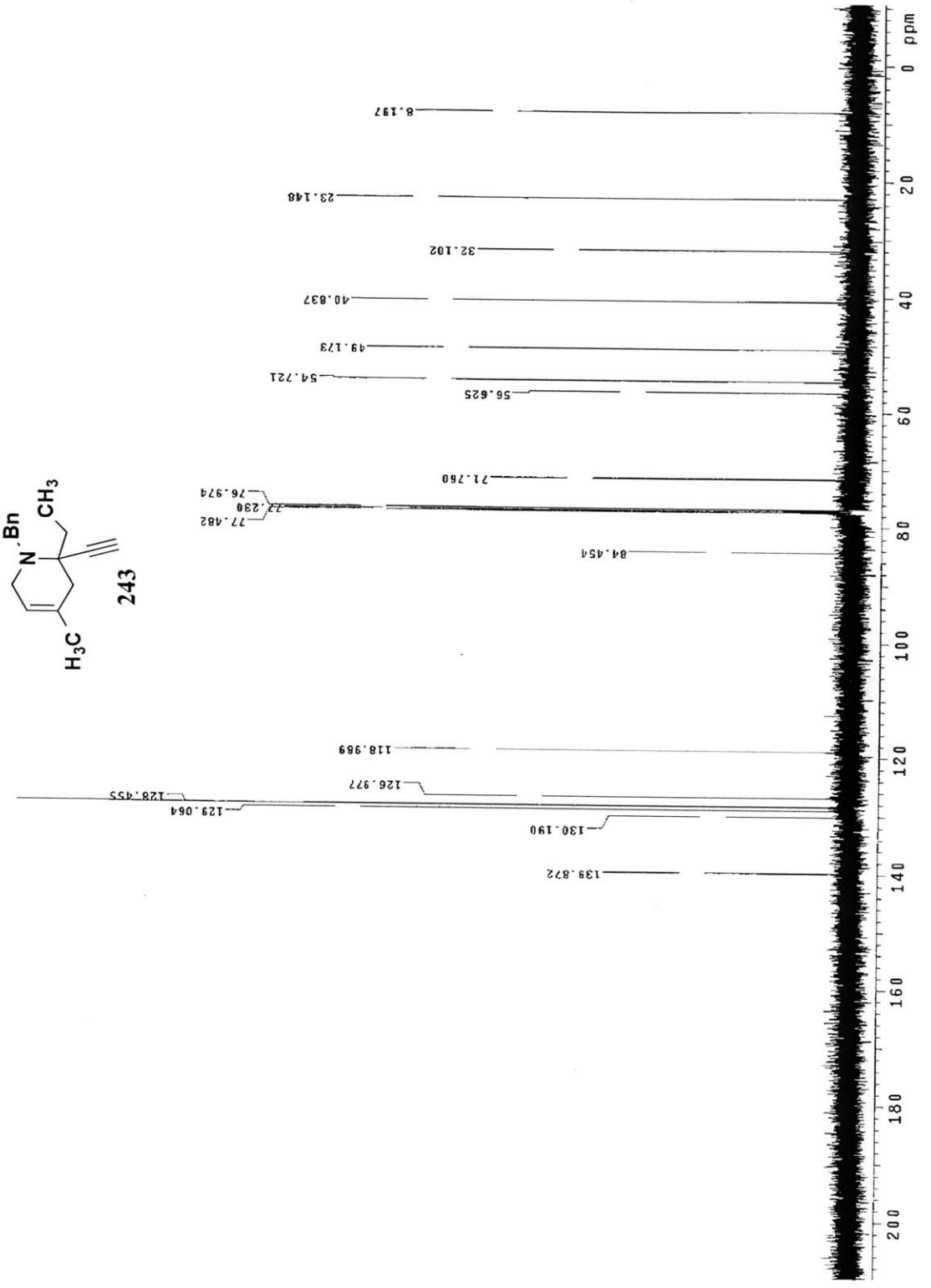
0.99 0.95
2.74


Bn
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CH3
H3C
243
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49.173
54.721
56.625
71.760
76.974
77.230
77.482
84.454
118.989
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40
60
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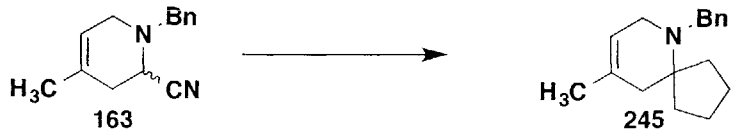
200

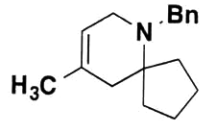


6-Benzyl-9-methyl-6-azaspiro[4.5]dec-8-ene (245). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.424 mL, 0.306 g, 3.02 mmol, 2.0 equiv) in 9 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.44 M in hexanes, 1.31 mL, 3.02 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **163** (0.320 g, 1.51 mmol, 1.0 equiv) in 3 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then a solution of $I(CH_2)_4OP(O)(OEt)_2$[12] (0.558 g, 1.66 mmol, 1.1 equiv) in 2 mL of THF was added dropwise via cannula over 2 min. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 mL of water and extracted with three 20-mL portions of ether. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.608 g of orange oil that was used immediately in the next step without further purification.

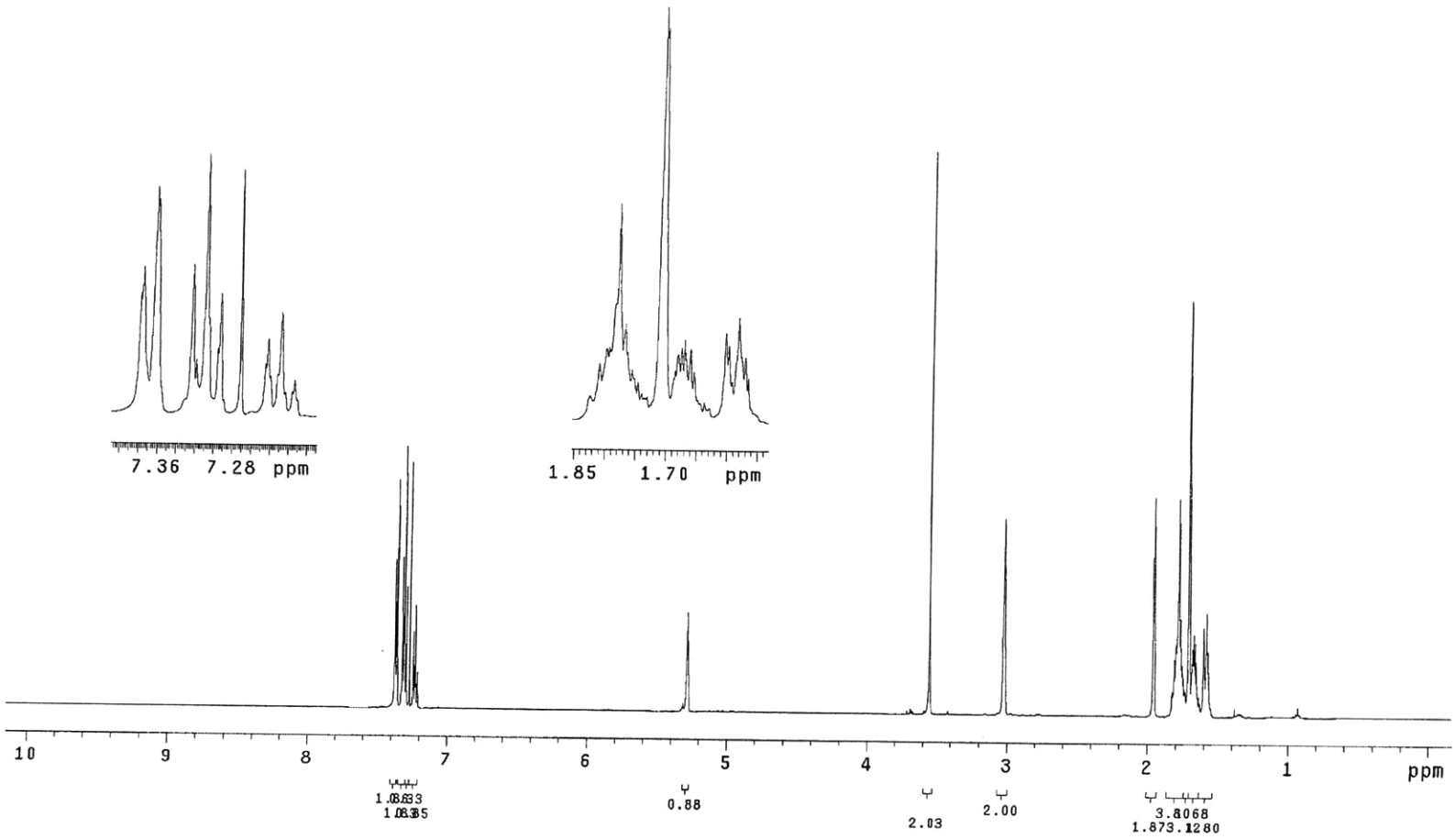
A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with 4,4′-di-*tert*-butylbiphenyl (1.217 g, 4.560 mmol, 3.0 equiv) and 12 mL of THF. Lithium ribbon (ca. 0.5-cm squares, 0.063 g, 9.1 mmol, 6.0 equiv) was added and the mixture was stirred at rt until a dark green color appeared (ca. 5 min). The reaction mixture was next cooled to 0 °C and stirred for 4 h. The resulting LiDBB solution was transferred via cannula into a 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper and the solution was cooled at -78 °C. A solution of the amino nitrile prepared above in 4 mL of THF was then added dropwise over 2 min. The reaction mixture was stirred at -78 °C for 10 min and then 2 mL of methanol was added dropwise over ca. 2 min. The

[12] Prepared from 4-iodo-butan-1-ol as described by Wolchenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745-2748.

reaction mixture was allowed to warm to room temperature and diluted with 20 mL of H_2O and extracted with three 20-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.890 g of an orange solid. Purification by column chromatography on 35 g of Et_3N-deactivated silica gel (elution with 2% EtOAc-benzene containing 1% Et_3N) afforded 0.164 g (45%) of **245** as a colorless oil: IR (thin film) 3025, 2955, 1603, 1452, 1338, 1150, and 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.23 (t, J = 8.0 Hz, 1 H), 5.28 (br s, 1 H), 3.55 (s, 2 H), 3.02 (s, 2 H), 1.95 (s, 2 H), 1.73-1.82 (m, 4 H), 1.71 (s, 3 H), 1.62-1.69 (m, 2 H), 1.56-1.60 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 132.3, 128.9, 128.3, 126.7, 118.4, 65.1, 54.3, 47.8, 38.6, 37.1, 24.7, 23.7; HRMS (m/z) $[M+H]^+$ calcd for $C_{17}H_{23}N$: 242.1903. Found: 242.1913.


N
Bn
H3C

245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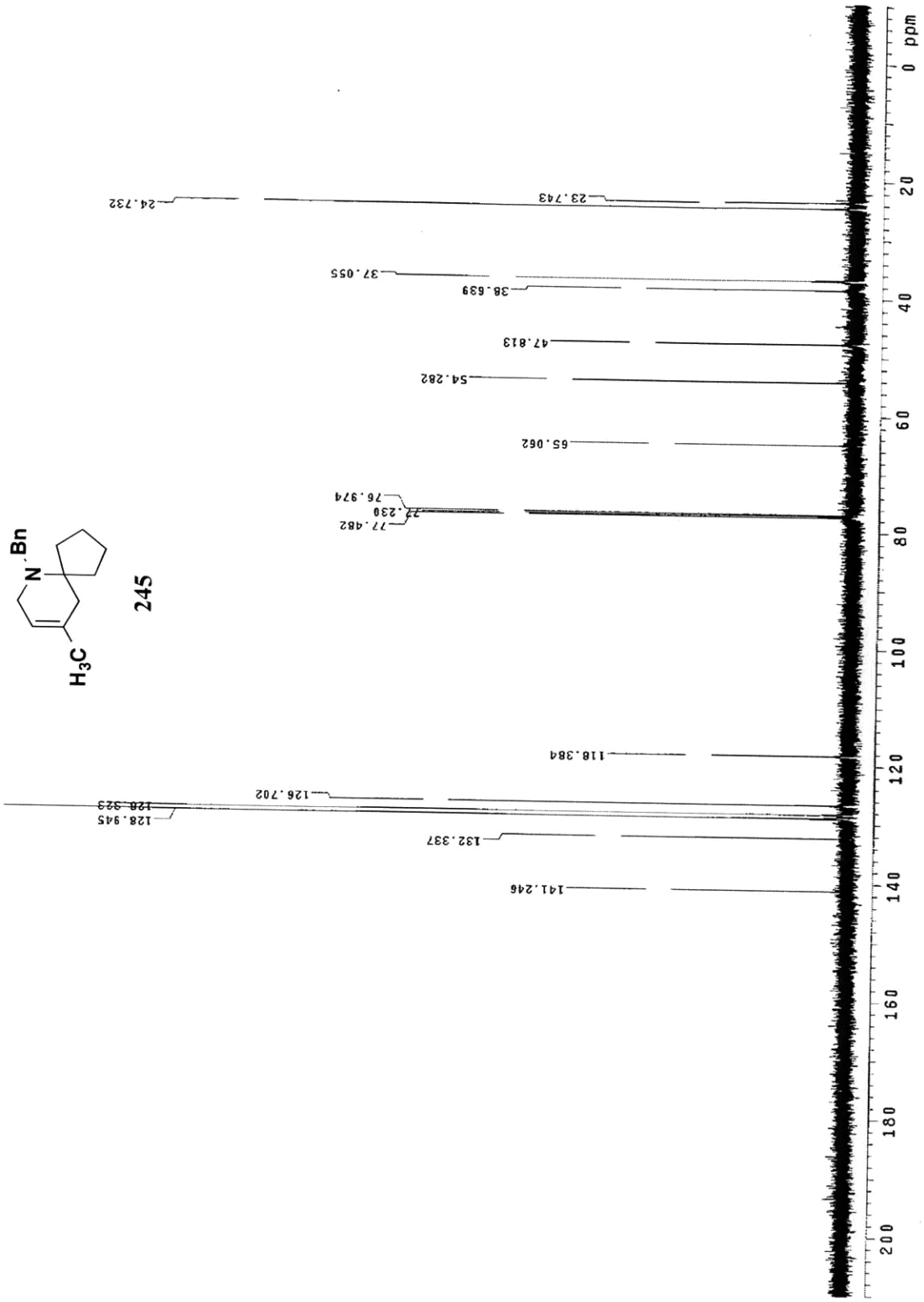
1.85 1.70 ppm
10
9
8
7
6
5
4
3
2
1
ppm
0.88
2.03
2.00
3.8068
1.873.1280


245
Bn
N
H3C
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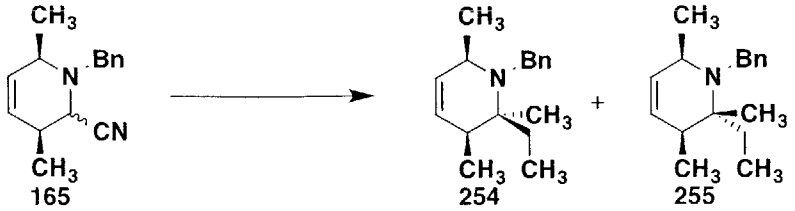
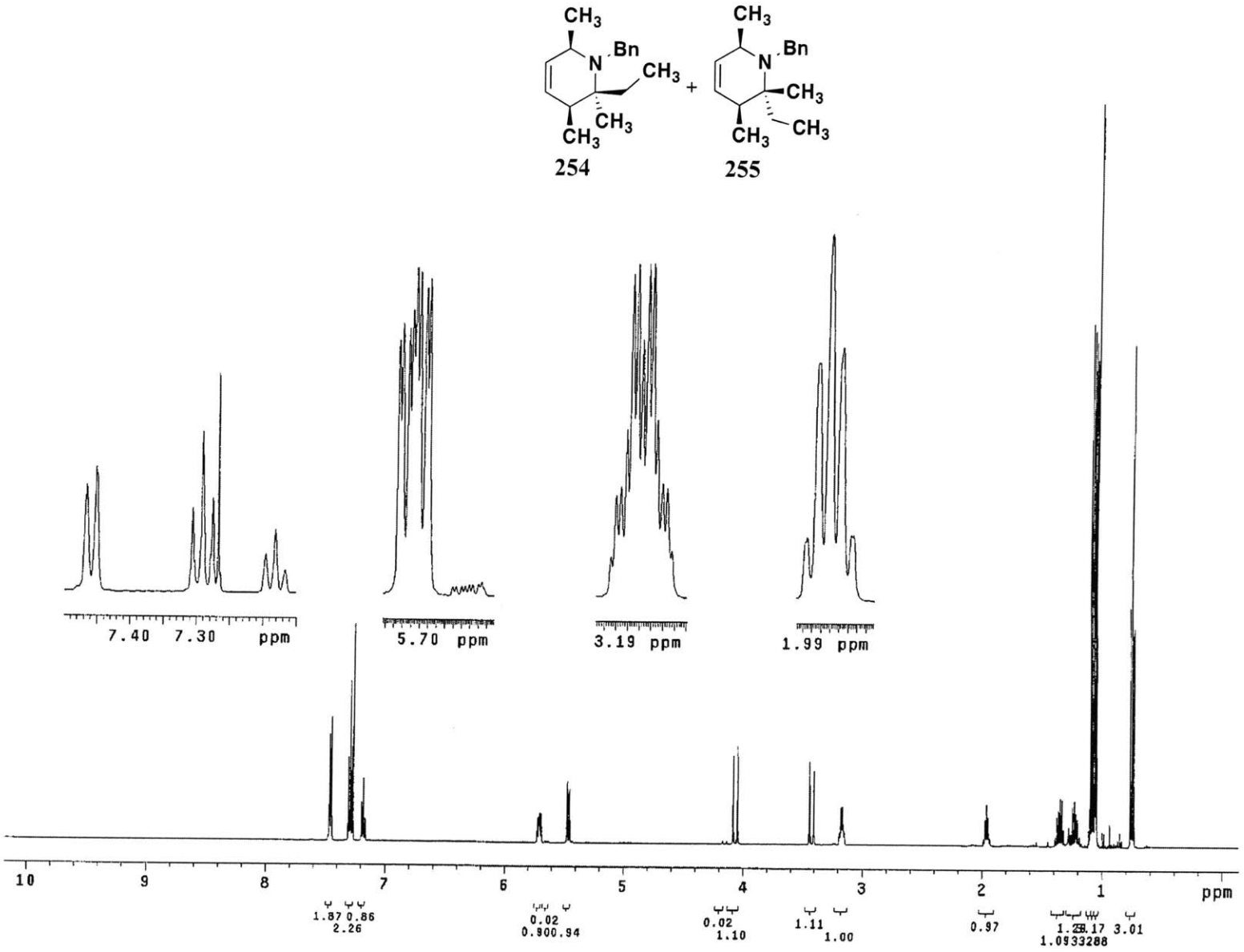
23.743
37.055
38.689
47.813
54.282
65.062
76.974
77.230
77.482
118.384
126.702
128.923
128.945
132.337
141.246
0 ppm
20
40
60
80
100
120
140
160
180
200



1-Benzyl-2-ethyl-2,3,6-trimethyl-1,2,3,6-tetrahydropyridine (254 and **255).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.187 mL, 0.135 g, 1.33 mmol, 2.0 equiv) in 4 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.31 M in hexanes, 0.574 mL, 1.33 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **165** (0.150 g, 0.663 mmol, 1.0 equiv) in 1.5 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.220 mL, 0.416 g, 2.65 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 12 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.159 g of a yellow oil that was used immediately in the next step without further purification.

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with $CeCl_3$ (0.741 g, 1.99 mmol, 3.0 equiv) and 6 mL of THF and the solution was stirred at rt for 2 h. The resulting mixture was cooled at -78 °C while methylmagnesium bromide (2.40 M solution in Et_2O, 0.829 mL, 1.99 mmol, 3.0 equiv) was added dropwise over 2 min. A solution of the amino nitrile prepared above in 1.5 mL of THF was then added dropwise over 2 min. The reaction mixture was allowed to warm to rt over 3 h, stirred at room temperature for 18 h, and then diluted with 15 mL of satd aq NH_4Cl solution. The aqueous layer was extracted with three 15-mL portions of Et_2O, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.128 g of an orange oil. Purification by column chromatography on

12 g of Et_3N-deactivated silica gel (elution with hexanes containing 1 % Et_3N) afforded 0.099 g (61%) of **254** (containing 2% of **255**) as a colorless oil: IR (thin film) 2969, 2929, 1605, 1452, 1368, 1110, and 738 cm^{-1}; For the major diastereomer **254** ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.5, 2 H), 7.29 (t, J = 7.5 Hz, 2 H), 7.18 (t, J = 7.0 Hz, 1 H) 5.71 (ddd, J = 10.0, 6.0, 2.0 Hz, 1 H), 5.46 (dd, J = 10.0, 2.0 Hz, 1 H), 4.06 (d, J = 17.5 Hz, 1 H), 3.42 (d, J = 17.5 Hz, 1 H), 3.17 (m, 1 H), 1.96 (m, 1 H), 1.35 (m, 1 H), 1.23 (m, 1 H), 1.09 (d, J = 6.5 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 1.05 (s, 3 H), 0.75 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 130.2, 129.3, 128.1, 127.0, 125.9, 58.7, 56.3, 52.7, 37.5, 30.1, 22.5, 16.8, 15.2, 8.1; HRMS (m/z) $[M+H]^+$ calcd for $C_{17}H_{25}N$: 244.2060. Found: 244.2052.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N
Bn
CH3
CH3
CH3
+
CH3
N
Bn
CH3
CH3
CH3
254
255
7.40 7.30 ppm
5.70 ppm
3.19 ppm
1.99 ppm
10
9
8
7
6
5
4
3
2
1
ppm
1.87 0.86
2.26
0.02
0.900.94
0.02
1.10
1.11
1.00
0.97
1.0933288
3.01

CH3
N
Bn
CH3
CH3
CH3
254
+
CH3
N
Bn
CH3
CH3
CH3
255
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129.623
129.147
128.973
128.712
128.538
128.455
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127.013
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58.585
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180
160
140
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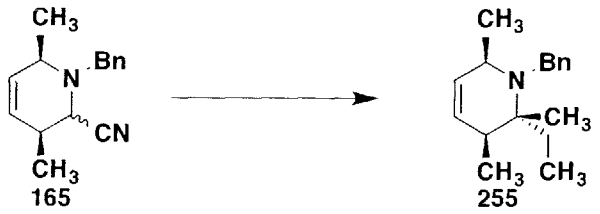
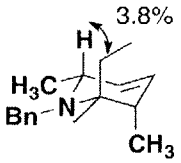
ppm



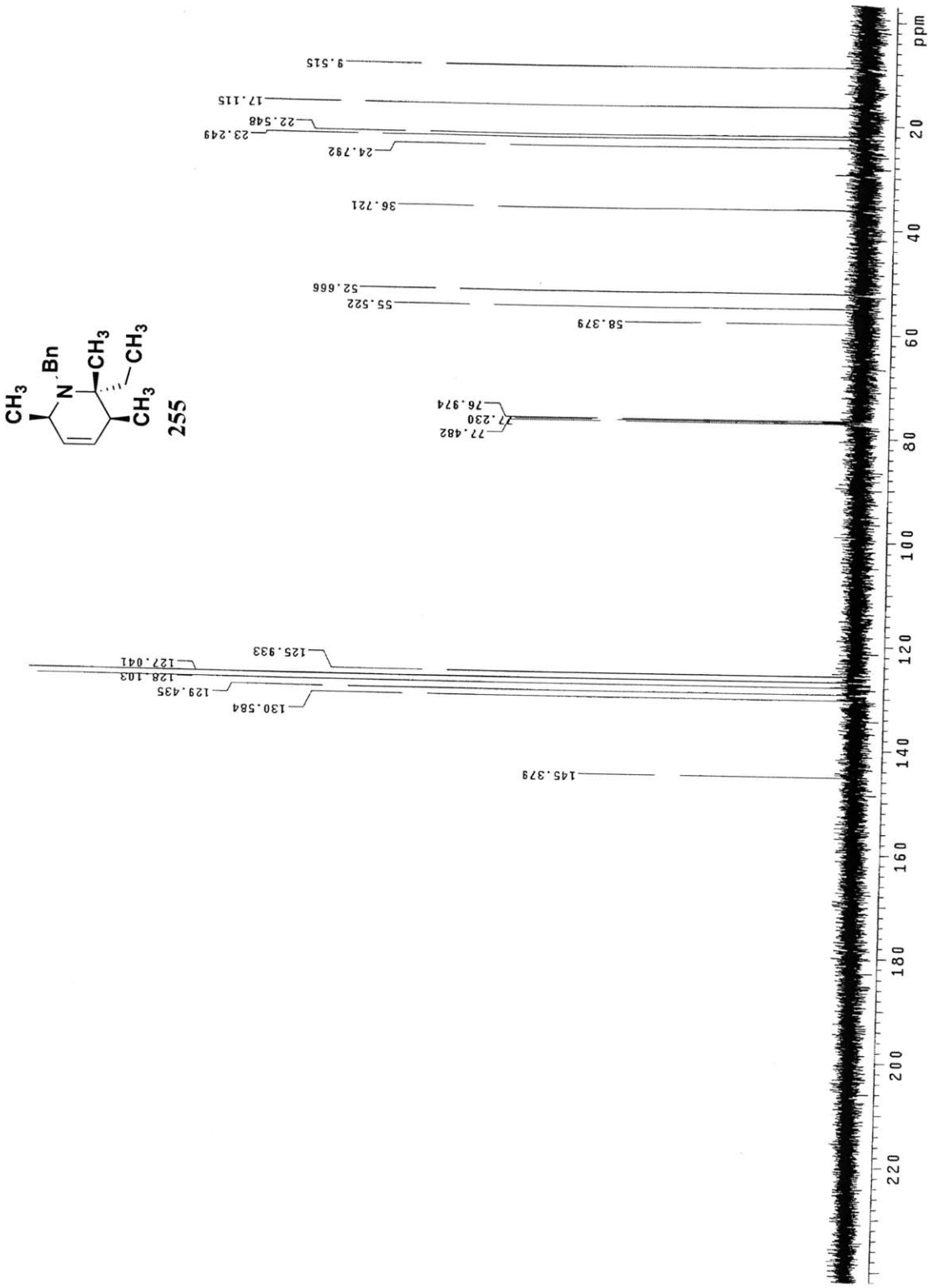
1-Benzyl-6-ethyl-2,5,6-trimethyl-1,2,5,6-tetrahydropyridine (255). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.212 mL, 0.151 g, 1.51 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.31 M in hexanes, 0.654 mL, 1.51 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **165** (0.171 g, 0.755 mmol, 1.0 equiv) in 1.5 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then methyl iodide (0.187 mL, 0.429 g, 3.02 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 12 mL of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.181 g of an orange oil that was used immediately in the next step without further purification.

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with $CeCl_3$ (0.846 g, 2.27 mmol, 3.0 equiv) and 6 mL of THF and the solution was stirred at rt for 2 h. The resulting mixture was cooled at -78 °C while ethylmagnesium bromide (2.40 M solution in Et_2O, 0.946 mL, 2.27 mmol, 3.0 equiv) was added dropwise over 2 min. A solution of the amino nitrile prepared above in 1 mL of THF was then added dropwise over 1 min. The reaction mixture was allowed to warm to rt over 3 h, stirred at room temperature for 16 h, and then diluted with 15 mL of satd aq NH_4Cl solution. The aqueous layer was extracted with three 15-mL portions of Et_2O, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.140 g of an orange oil. Purification by column chromatography on

12 g of Et_3N-deactivated silica gel (elution with hexanes containing 1 % Et_3N) afforded 0.103 g (56%) of **255** as a light yellow oil: IR (thin film) 2969, 2929, 1605, 1452, 1368, 1110, and 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.0 Hz, 2 H), 7.29 (t, J = 7.0 Hz, 2 H), 7.18 (t, J = 7.0 Hz, 1 H), 5.64 (ddd, J = 10.0, 5.5, 1.9 Hz, 1 H), 5.44 (dd, J = 10.0, 1.9 Hz, 1 H), 4.15 (d, J = 17.0 Hz, 1 H), 3.43 (d, J = 17.0 Hz, 1 H), 3.23 (m, 1 H), 2.08 (m, 1 H), 1.78 (m, 1 H), 1.57 (m, 1 H), 1.10 (d, J = 6.5 Hz, 3 H), 0.99 (d, 7.0 Hz, 3 H), 0.93 (s, 3 H), 0.85 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 130.6, 129.4, 128.1, 127.0, 125.9, 58.4, 55.5, 52.7, 36.7, 24.8, 23.2, 22.5, 17.1, 9.5; HRMS (m/z) $[M+H]^+$ calcd for $C_{17}H_{25}N$: 244.2060. Found: 244.2052. The assignment of stereochemistry is based on a differential NOE experiment (500 MHz, $CDCl_3$): 3.2% from 3.23 ppm to 1.78 ppm



CH3
N
Bn
CH3
CH3
CH3
255
ppm
ppm
3.25 ppm
9
8
7
6
5
4
3
2
1
ppm
1.92 1.03
3.56
0.97
0.97
1.03
1.00
1.01
1.04
1.02
1.13
2.62
2.59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58.379
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77.230
77.482
125.933
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145.379
ppm
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80
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120
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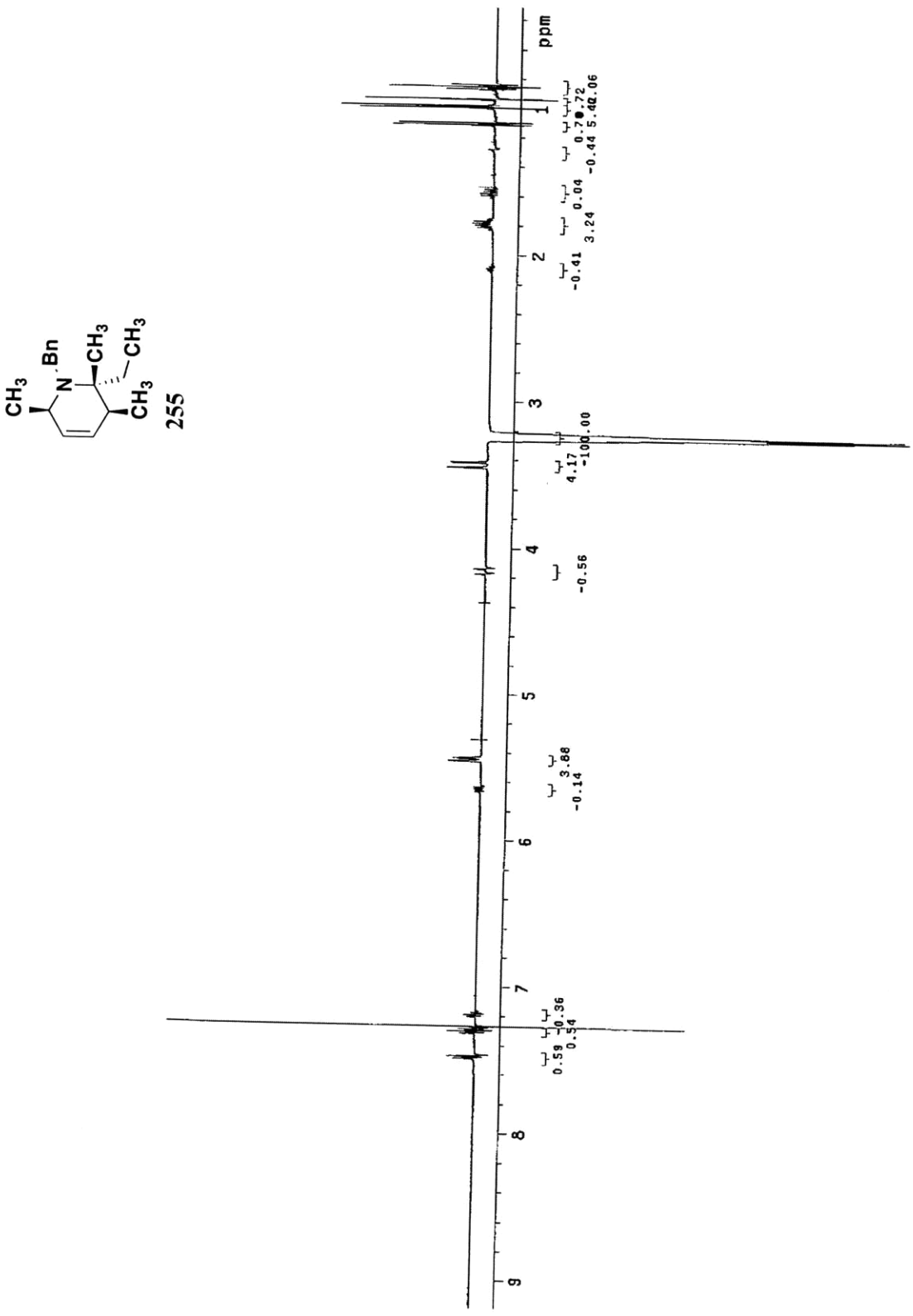
200
220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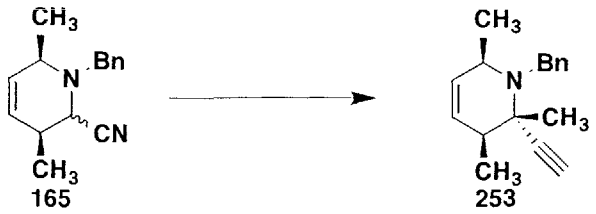
Bn
N
CH3
CH3
CH3
255
ppm
1
2
3
4
5
6
7
8
9
0.72
5.42.06
0.79
-0.44
0.04
3.24
-0.41
4.17
-100.00
-0.56
3.88
-0.14
0.59
-0.36
0.54

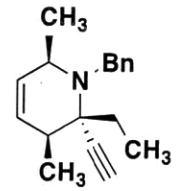


1-Benzyl-2-ethyl-2-ethynyl-3,6-dimethyl-1,2,3,6-tetrahydropyridine (253). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of diisopropylamine (0.170 mL, 0.123 g, 1.22 mmol, 2.0 equiv) in 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.44 M in hexanes, 0.500 mL, 1.22 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **165** (0.138 g, 0.610 mmol, 1.0 equiv) in 1 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.195 mL, 0.381 g, 2.44 mmol, 4.0 equiv) was added rapidly dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 10 mL of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of satd NaCl solution, dried over K_2CO_3, filtered, and concentrated to give 0.156 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the amino nitrile prepared above in 4 mL of Et_2O. The solution was cooled at -78 °C while ethynylmagnesium bromide solution (0.50 M in THF, 3.66 mL, 1.83 mmol, 3.0 equiv) was added dropwise over 3 min. The reaction mixture was allowed to warm to rt over 3.5 h, stirred at rt for 16 h, and then diluted with 5 mL of satd aq NH_4Cl solution and 5 mL of water. The aqueous layer was extracted with three 15-mL portions of ether, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.152 g of an orange oil. Column chromatography on 15 g of Et_3N-deactivated silica gel (elution with

hexanes containing 1% Et_3N) afforded 0.117 g (76%) of **253** as a yellow oil:[13] IR (thin film) 3300, 3028, 2973, 2938, 1452, 1100, 739, and 638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.20 (t, J = 8.0 Hz, 1 H), 5.77 (ddd, J = 10.0, 6.0, 0.5 Hz, 1 H), 5.58 (ddd, J = 10.0, 2.4, 0.5 Hz, 1 H), 4.07 (d, J = 17.5 Hz, 1 H), 3.60 (d, J = 17.5 Hz, 1 H), 3.29 (m, 1 H), 2.32 (m, 1 H), 2.24 (s, 1 H), 1.55 (dq, J = 15.0, 7.0 Hz, 1 H), 1.20 (m, 1 H), 1.20 (d, J = 6.5 Hz, 3 Hz), 1.05 (d, J = 6.5 Hz, 3 H), 0.89 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 130.8, 128.4, 128.2, 126.9, 126.1, 86.0, 70.3, 62.0, 57.1, 54.4, 37.0, 30.0, 22.0, 15.6, 8.6; HRMS (m/z) $[M+H]^+$ calcd for $C_{18}H_{23}N$: 254.1903. Found: 254.1910.

[13] Stereochemical assignment of the quaternary center was made based on the similar reaction where **254** is formed diastereoselectively.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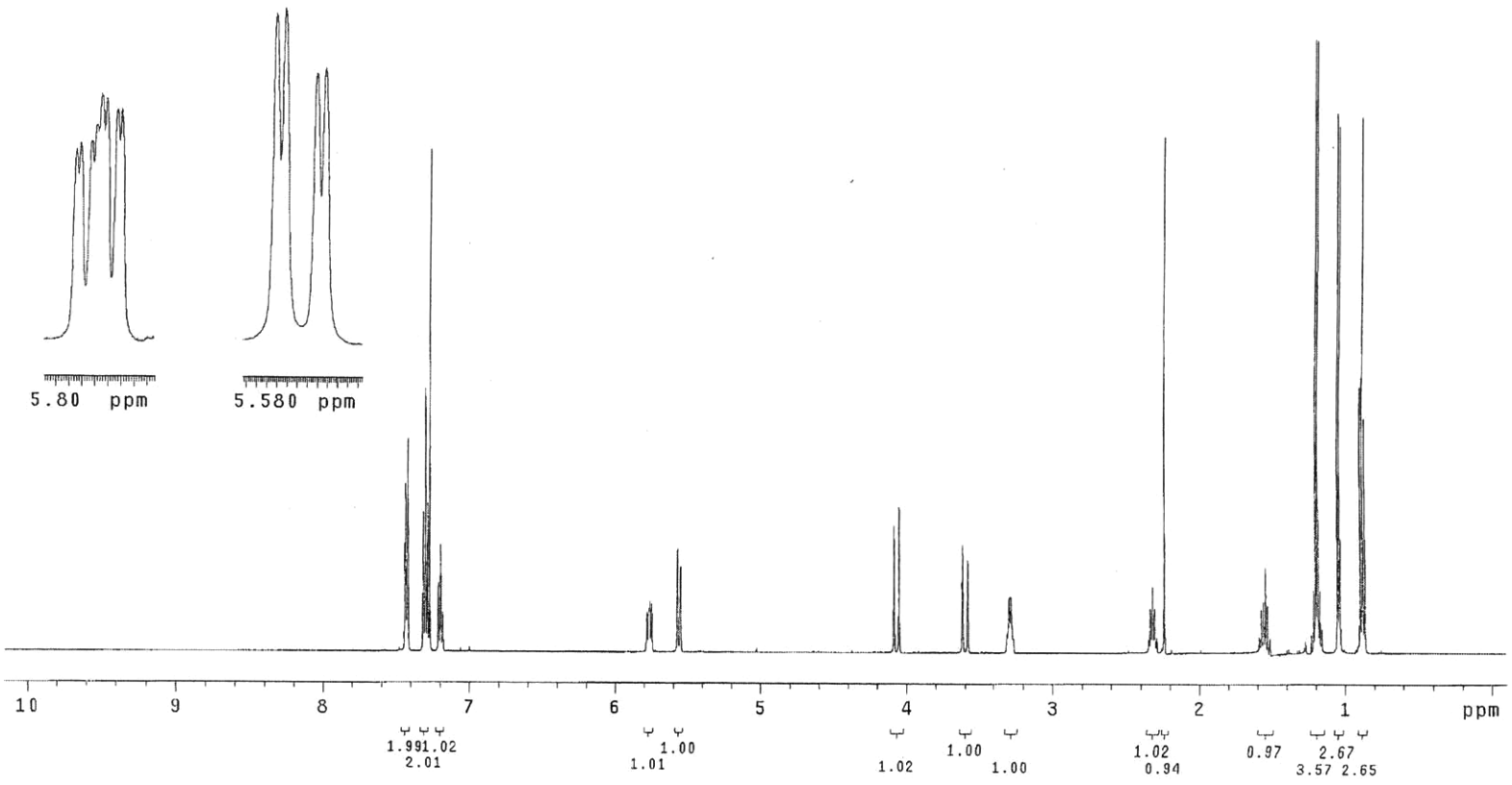
Bn
N
CH3
CH3

253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7
6
5
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2
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ppm
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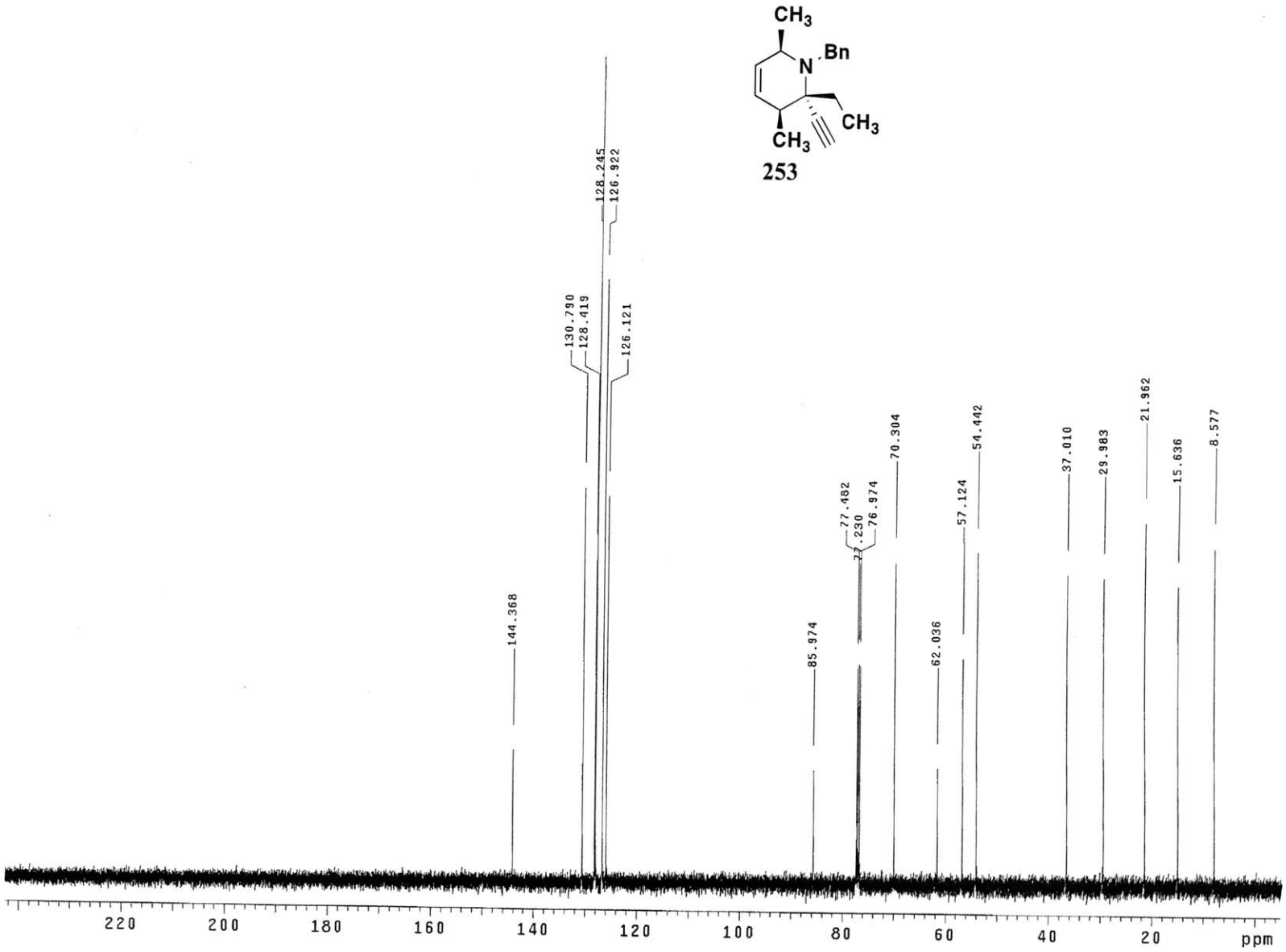
1.02
1.00 1.00
1.02 0.94
0.97
2.67 3.57 2.65


CH3
N
Bn
CH3
CH3
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128.245
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126.121
85.974
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77.230
76.974
70.304
62.036
57.124
54.442
37.010
29.983
21.962
15.636
8.577
220
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140
120
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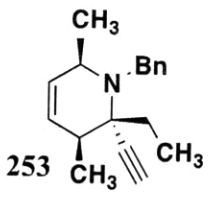
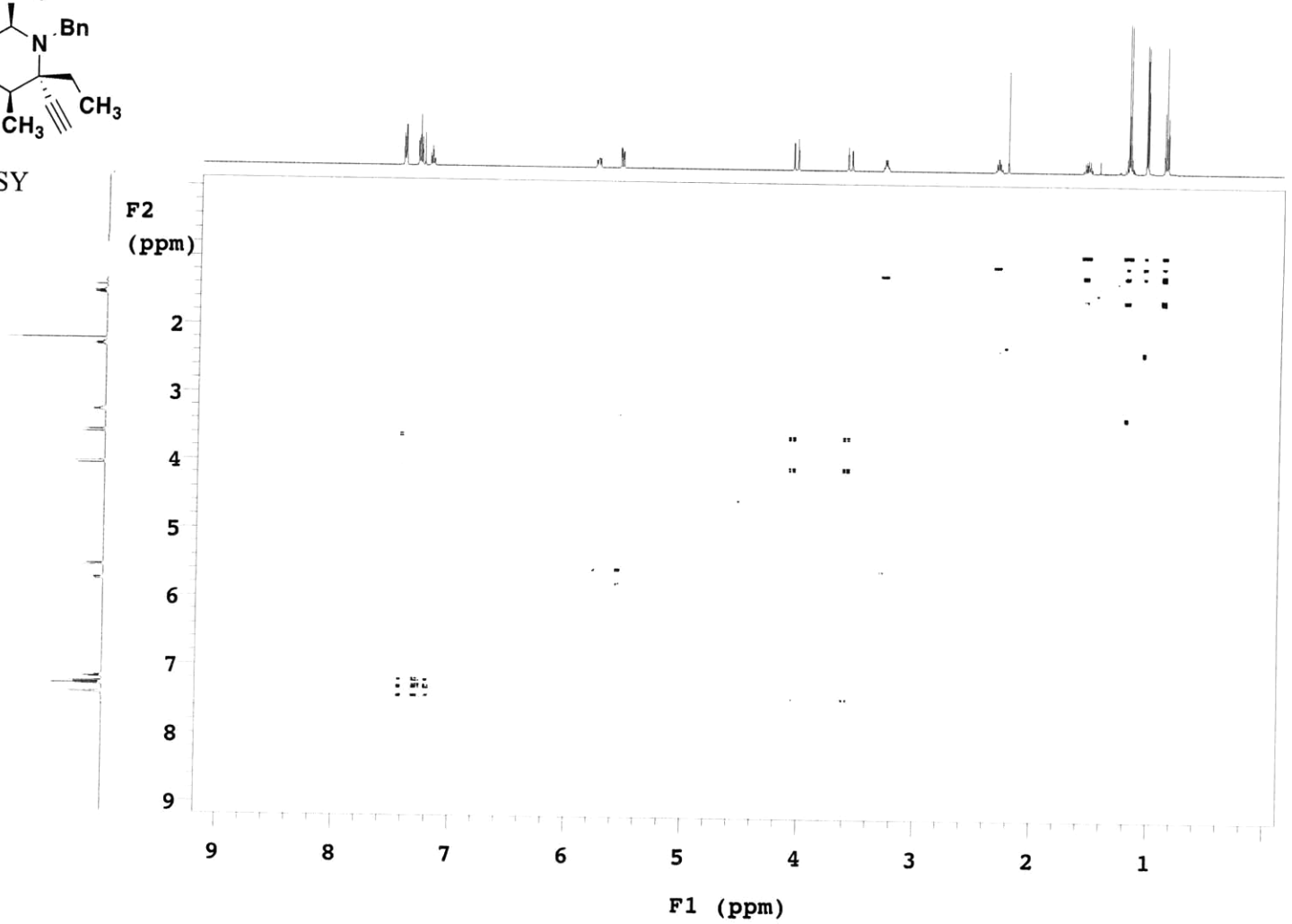
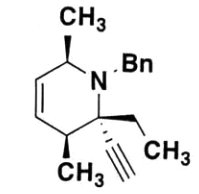
80
60
40
20
ppm



253

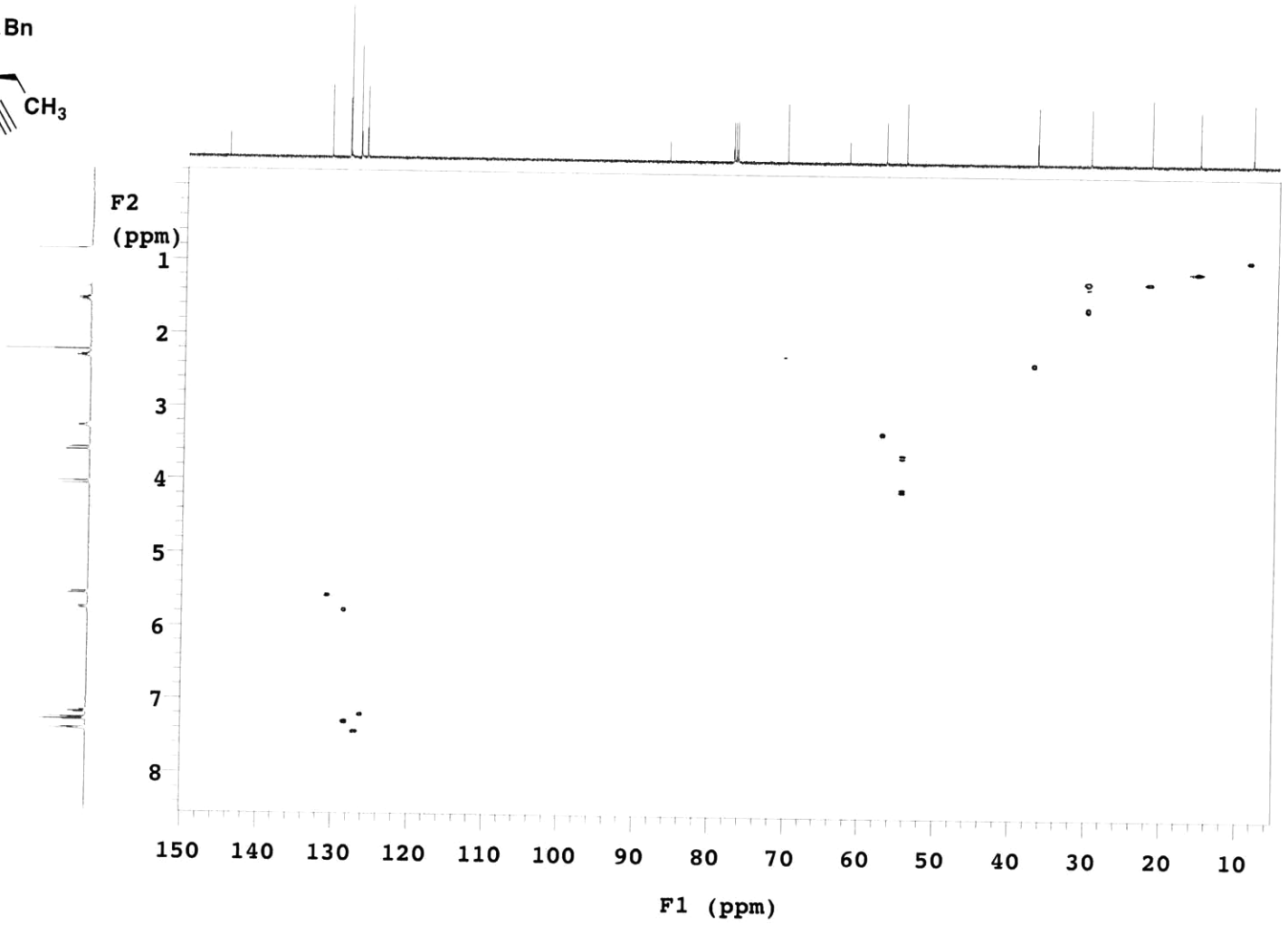
gCOSY




CH3
N
Bn
CH3
CH3

253

HSQC


F2
(ppm)
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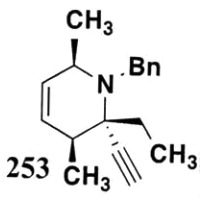
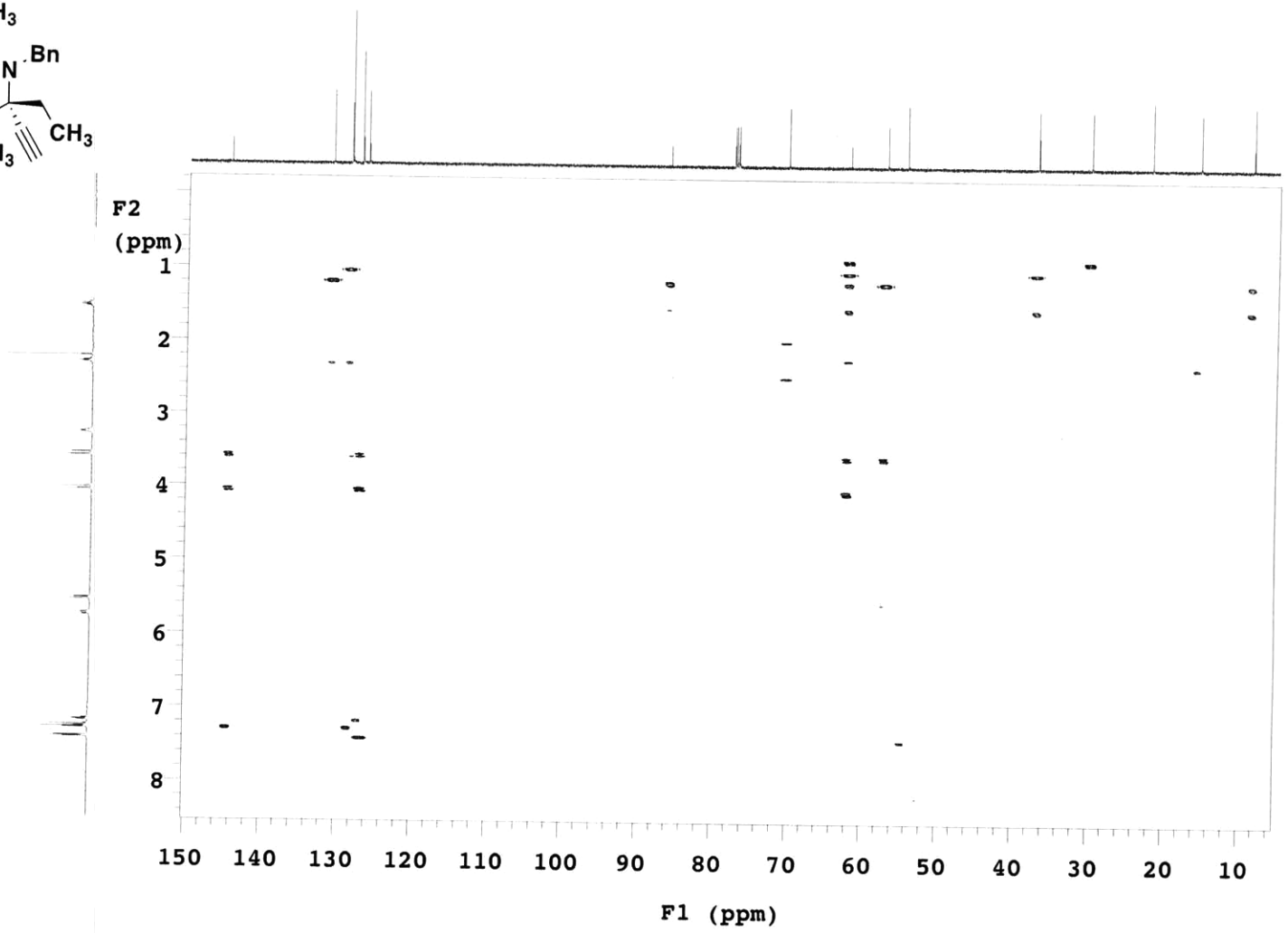
2
3
4
5
6
7
8
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
F1 (ppm)

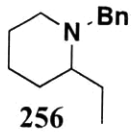

CH3
Bn
N
253
CH3
CH3

HMBC

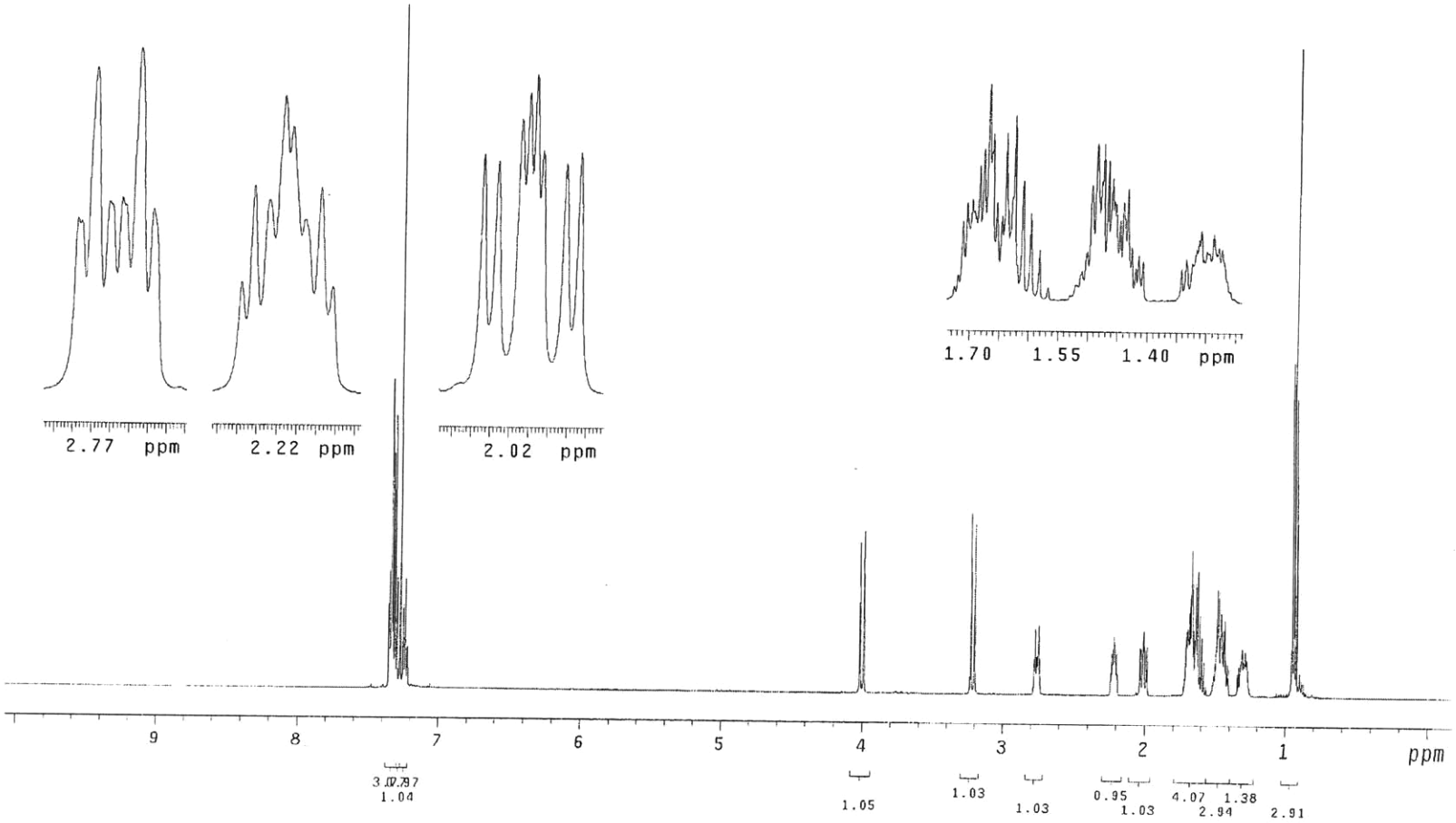

F2
(ppm)
1
2
3
4
5
6
7
8
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
F1 (ppm)

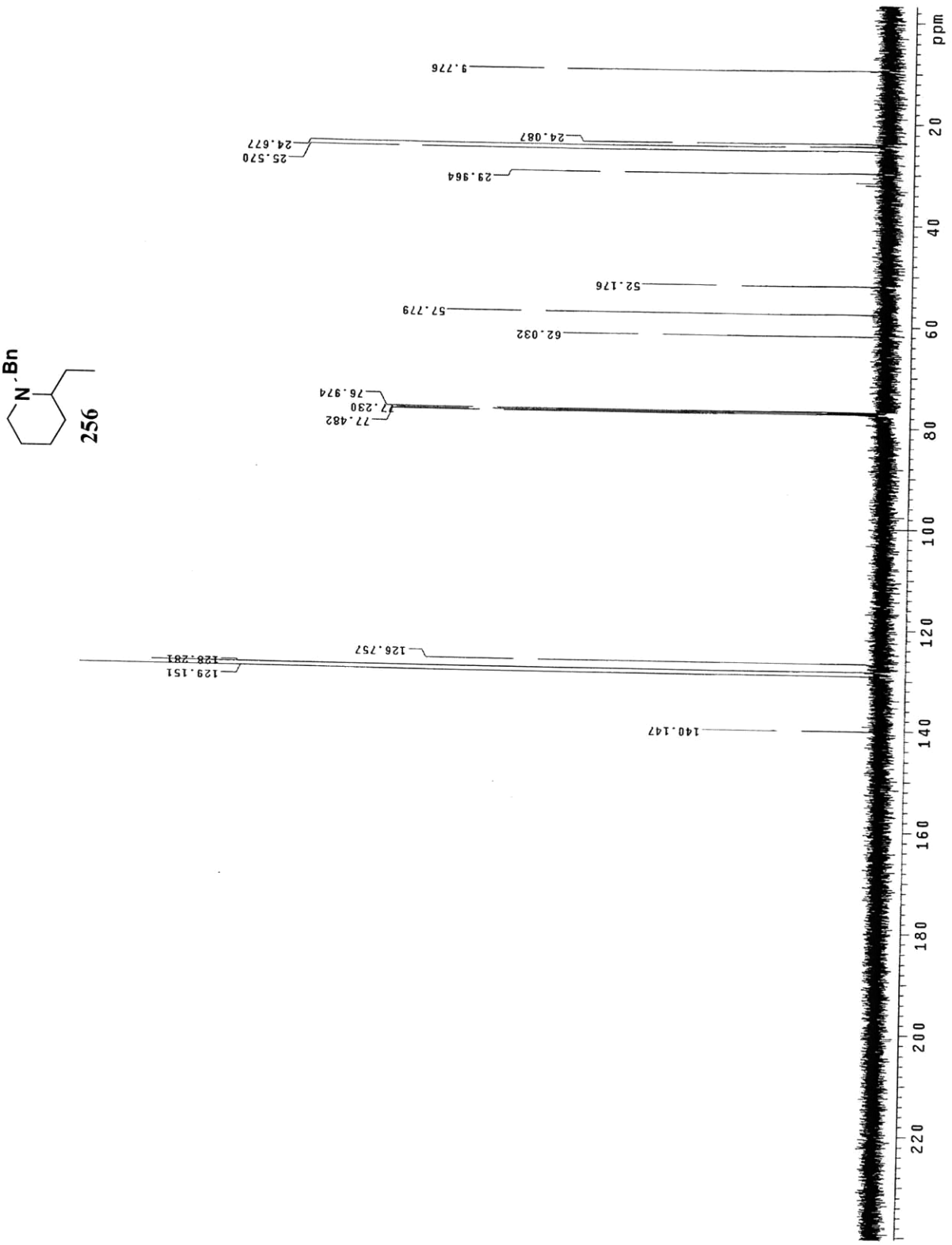
1-Benzyl-2-ethylpiperidine (256). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a slurry of ca. 2.60 g of activated Raney nickel[14] in ca. 3 mL of acetone. A solution of vinyl sulfide **181** (0.265 g, 0.86 mmol, 1.0 equiv) in 2 mL of acetone was then added rapidly via cannula and the septum was removed and replaced with a reflux condenser fitted with a rubber septum and argon inlet needle. The reaction mixture was heated at reflux for 3.5 h and then cooled to rt. The resulting heterogeneous mixture was filtered through a 1-in pad of Celite in a Buchner funnel with the aid of 35 mL of acetone and the filtrate was concentrated at 100 mmHg. Purification by column chromatography on 18 g of silica gel (elution with 4% Et_2O-pentane containing 1% Et_3N) afforded 0.125 g (71%) of **256** as a colorless oil: IR (thin film) 3026, 2932, 2788, 1945, 1872, 1806, 1452, 1067, 733, and 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.21-7.35 (m, 5 H), 4.00 (d, J = 13.5 Hz, 1 H), 3.21 (d, J = 13.5 Hz, 1 H), 2.75 (dt, J = 11.0 4.0 Hz, 1 H), 2.21 (ddt, J = 9.0, 7.5, 3.3 Hz, 1H), 2.01 (ddd, J = 11.5, 10.0, 4.0 Hz, 1 H), 1.57-1.72 (m, 4 H), 1.41-1.51 (m, 3 H), 1.27-1.34 (m, 1 H), 0.94 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1, 129.1, 128.3, 126.8, 62.0, 57.8, 52.2, 30.0, 25.6, 24.7, 24.1, 9.8; HRMS (m/z) $[M+H]^+$ calcd for $C_{14}H_{21}N$: 204.1747. Found: 204.1744.

[14] The mass of Raney nickel (WR Grace Grade 28) was determined by the following procedure: The mass of a 5-mL volumetric flask containing 5 mL of water was recorded (Mass 1). A slurry of Ra-Ni in water was transferred to the volumetric flask via pipet after removal of ca 2.5 mL water from the flask and the mass was recorded (Mass 2). The mass of Ra-Ni was calculated using: Mass = 1.167(Mass 1 – Mass 2). The slurry was then transferred to the reaction flask and the excess water was removed via cannula. The remaining Ra-Ni was washed with four 5-mL portions of acetone via cannula.


N
Bn

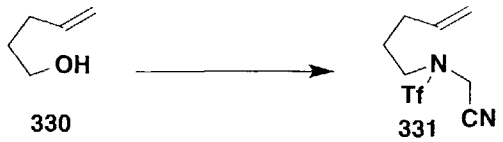
256


2.77 ppm
2.22 ppm
2.02 ppm
1.70 1.55 1.40 ppm
9
8
7
6
5
4
3
2
1
ppm
1.04
1.05
1.03
1.03
0.95
1.03
4.07
1.38
2.94
2.91


Bn
N
256
9.776
24.087
24.677
25.570
29.964
52.176
57.779
62.032
76.974
77.230
77.482
126.757
128.281
129.151
140.147
ppm
20
40
60
80
100
120
140
160
180
200
220

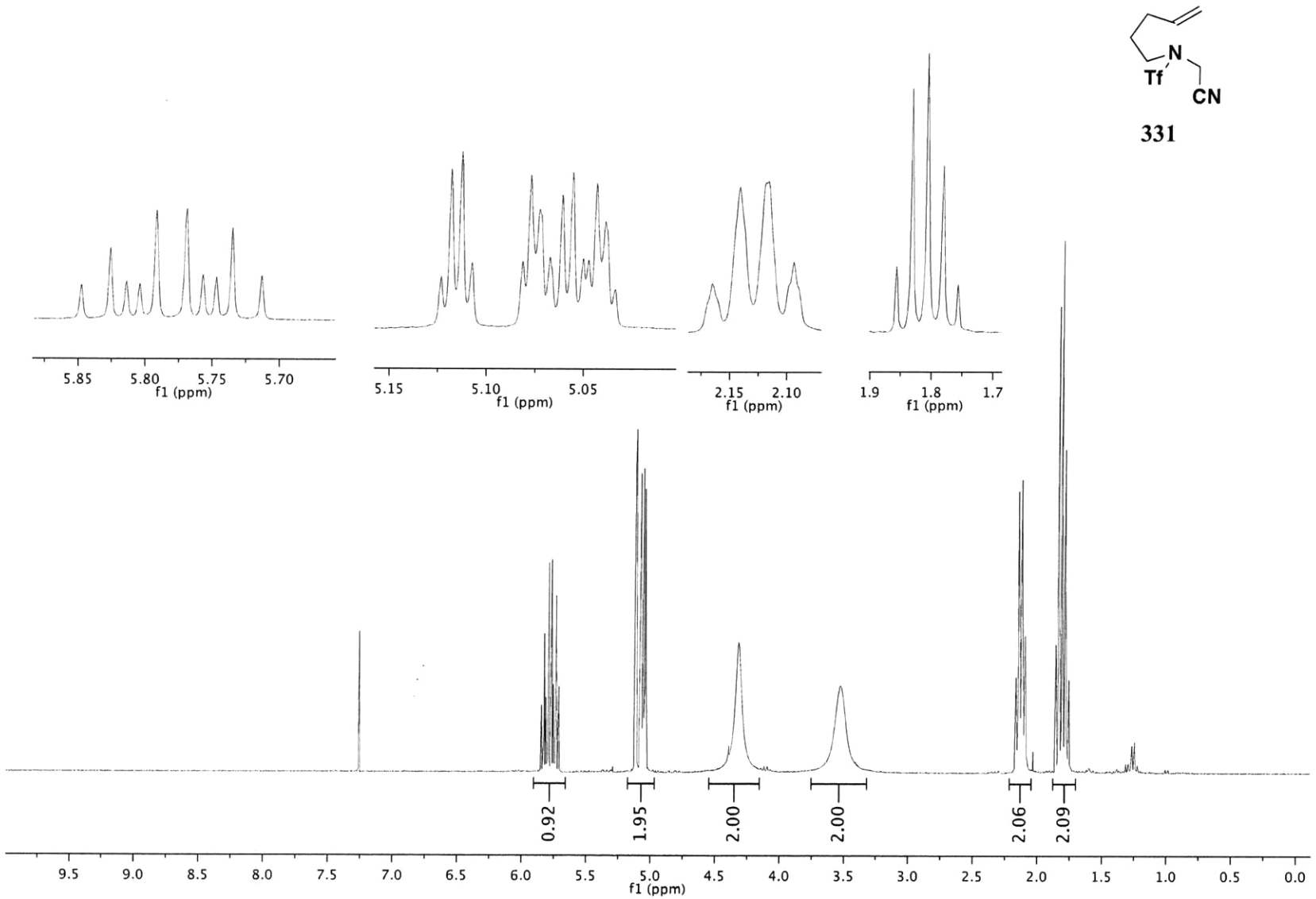
Total Synthesis

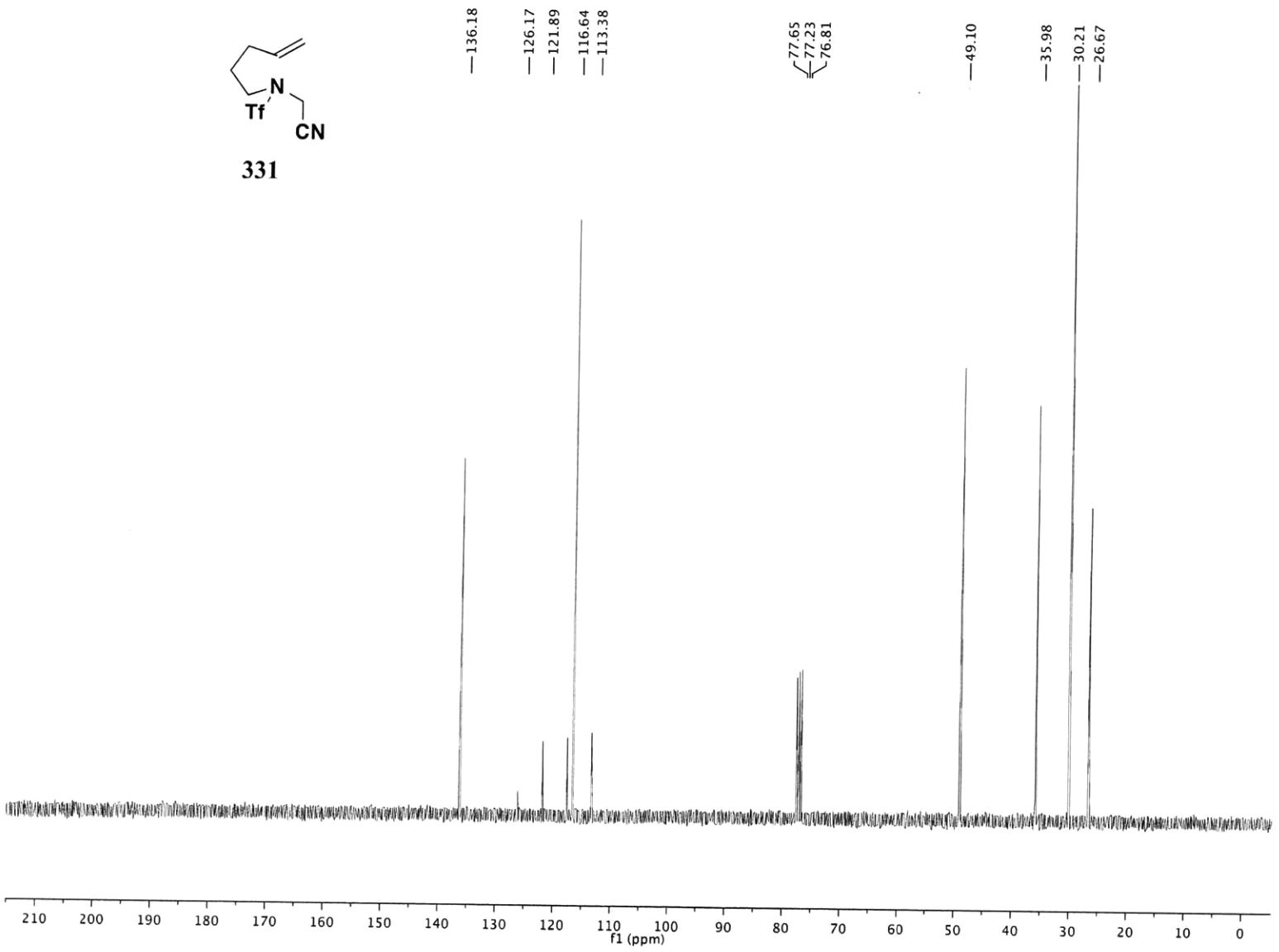
Experimentals and Spectra

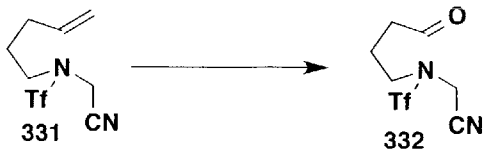


330 331

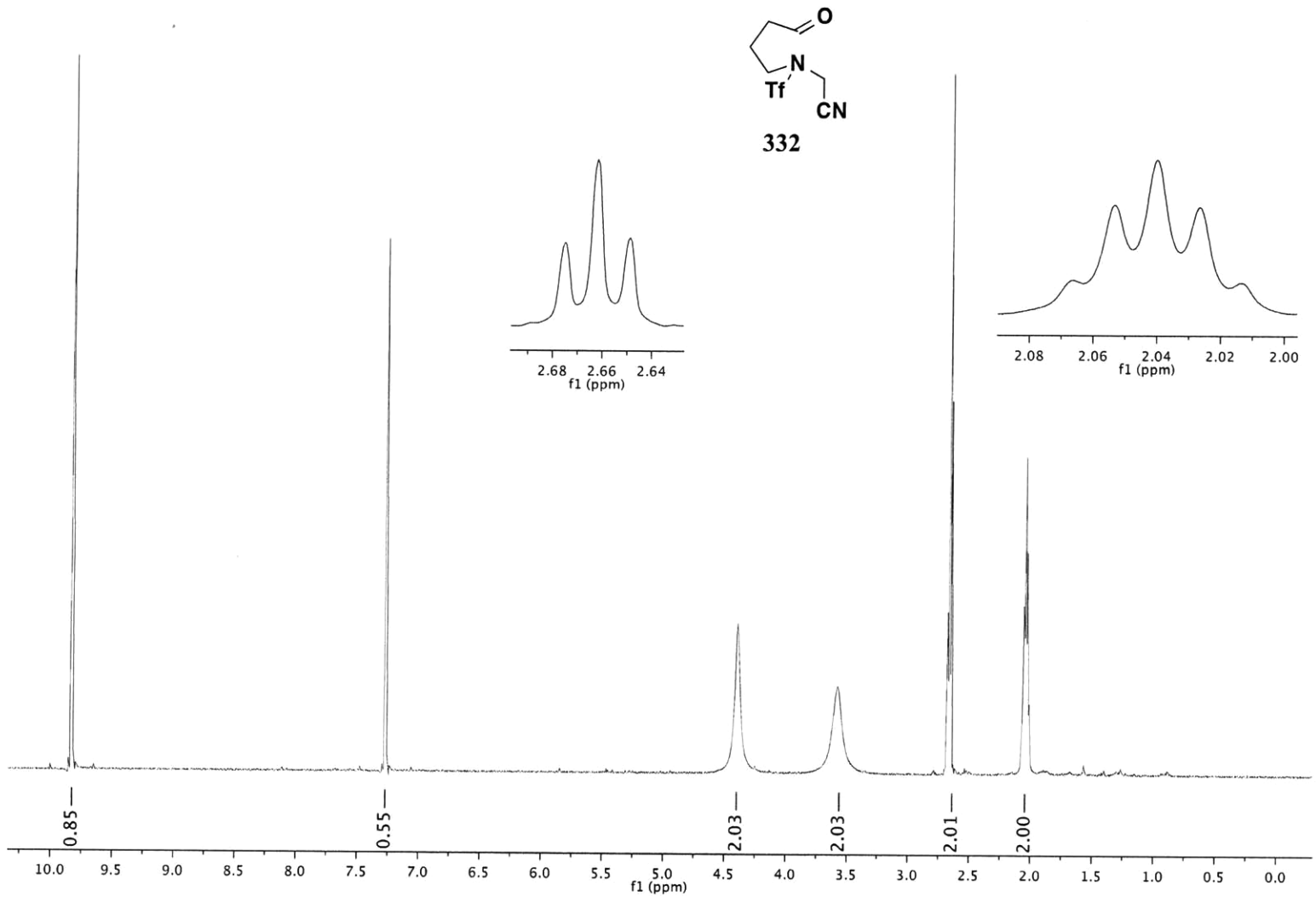
***N*-(Cyanomethyl)-*N*-(4-pentenyl)trifluoromethanesulfonamide (331).** A 100-mL, round-bottomed flask equipped with a rubber septum fitted with an argon inlet needle was charged with triphenylphosphine (7.76 g, 29.1 mmol, 1.1 equiv), 50 mL of THF, and $TfNHCH_2CN$ (5.31 g, 28.3 mmol, 1.05 equiv). 4-penten-1-ol (2.76 mL, 2.32 g, 26.9 mmol, 1.0 equiv) was then added in one portion, and DIAD (5.73 mL, 5.98 g, 29.6 mmol, 1.1 equiv) was added dropwise by syringe over 20 min. The resulting mixture was stirred at rt for 3 h and then concentrated to give 23.32 g of a yellow solid. A solution of this material in 80 mL of CH_2Cl_2 was concentrated onto 35 g of silica gel and transferred to the top of a column of 230 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes yielded 6.684 g (97%) of **331** as a yellow oil: IR (film): 3083, 2995, 2946, 1643, 1397, 1286, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.2, 6.6 Hz, 1 H), 5.05-5.13 (m, 2H), 4.35 (br s, 2 H), 3.58 (br s, 2 H), 2.14 (app q, J = 7.0 Hz, 2 H), 1.82 (quint, J = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 119.8 (q, J = 322 Hz), 116.7, 113.5, 49.2, 36.0, 30.3, 26.7; Anal. Calcd for $C_8H_{11}F_3N_2O_2S$: C, 37.50; H, 4.33; N, 10.93. Found: C, 37.37; H, 4.27; N, 11.03.


N
Tf
CN
331
5.85
5.80
5.75
5.70
f1 (ppm)
5.15
5.10
5.05
f1 (ppm)
2.15
2.10
f1 (ppm)
1.9
1.8
1.7
f1 (ppm)
0.92
1.95
2.00
2.00
2.06
2.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

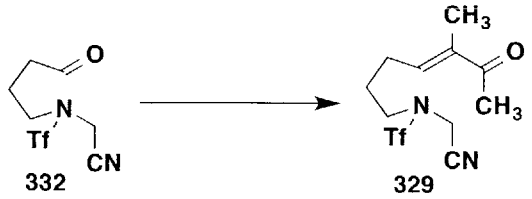

N
Tf
CN
331
136.18
126.17
121.89
116.64
113.38
77.65
77.23
76.81
49.10
35.98
30.21
26.67
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



***N*-(Cyanomethyl)-*N*-(4-heptenal)trifluoromethanesulfonamide (332).** A 250-mL, round-bottomed flask containing triflamide **331** (6.007 g, 23.44 mmol, 1.0 equiv) was fitted with a rubber septum and argon-inlet needle and purged with argon. CH_2Cl_2 (100 mL) was added, and the flask was cooled at –78 °C while ozone was bubbled through the solution for 40 min. The resulting blue solution was purged with a stream of argon for 20 min. Triphenylphosphine (6.149 g, 23.44 mmol, 1.0 equiv) was added as a solid, and the solution was allowed to slowly warm to rt over 15 h. Concentration by rotary evaporation afforded 14.852 g of a cloudy, white oil. A solution of this material in 50 mL of CH_2Cl_2 was concentrated onto 30 g of silica gel and transferred to the top of a column of 150 g of silica gel. Elution with 10-35% EtOAc-hexanes provided 5.129 g (85%) of **332** as a white solid: mp: 52-53 °C; IR (KBr): 3006, 2956, 2848, 2746, 2260, 1723, 1464, 1387, 1366, 1232, 1192, 1139, 1111, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 4.40 (br s, 2H), 3.58 (br s, 2 H), 2.66 (t, J = 6.5 Hz, 2 H), 2.04 (p, J = 6.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.3, 119.8 (q, J = 323 Hz), 48.8, 40.2, 35.9, 19.4; Anal. Calcd for $C_7H_9F_3N_2O_3S$: C, 32.56; H, 3.51; N, 10.85. Found: C, 32.76; H, 3.35; N, 10.69.


O
N
Tf
CN
332
2.68 2.66 2.64
f1 (ppm)
2.08 2.06 2.04 2.02 2.00
f1 (ppm)
0.85
0.55
2.03
2.03
2.01
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

200.33
123.61
121.05
118.49
115.92
113.35
77.48
77.23
76.98
48.82
40.15
35.89
19.41
O
N
Tf
CN
332
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)

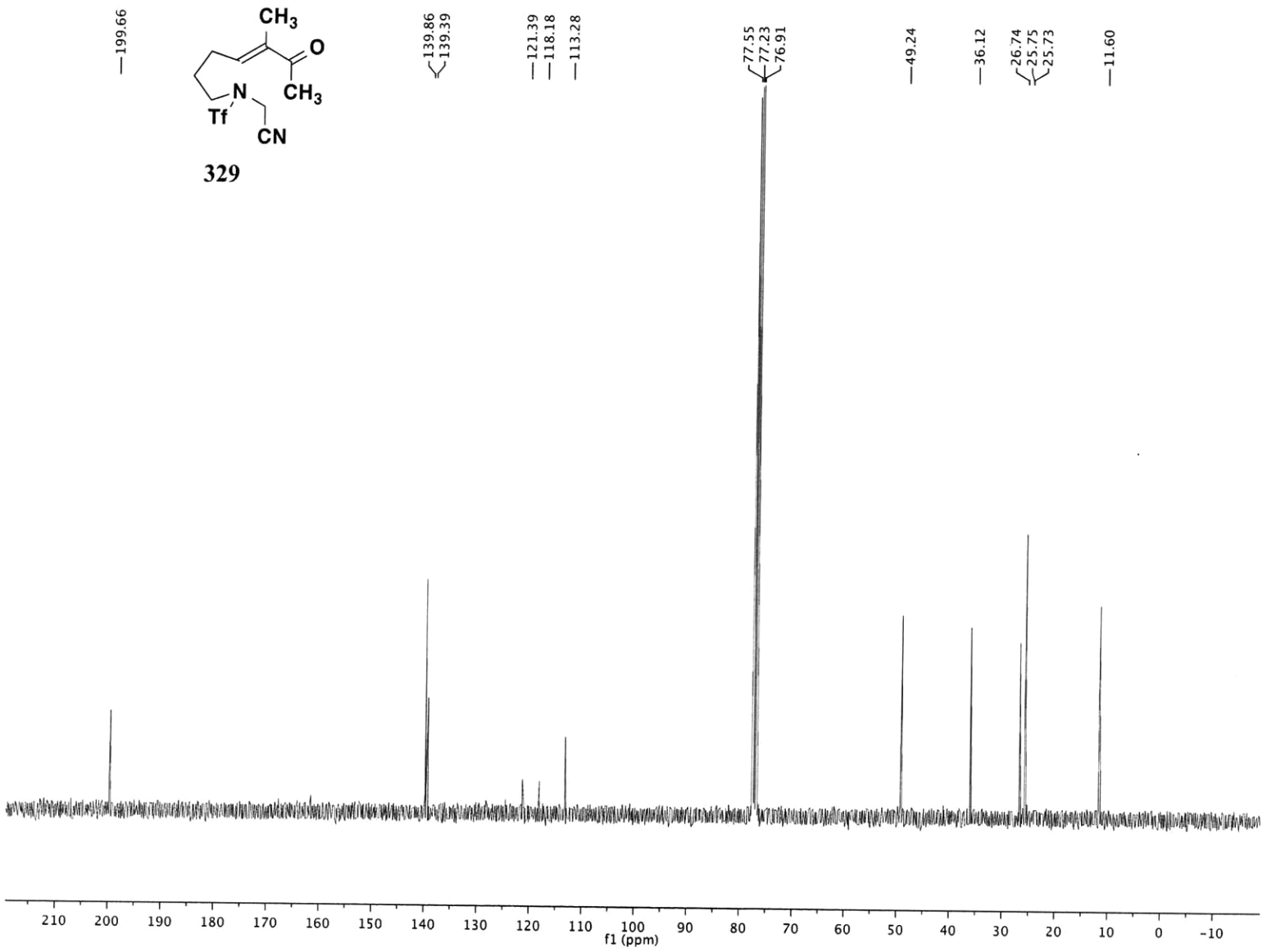


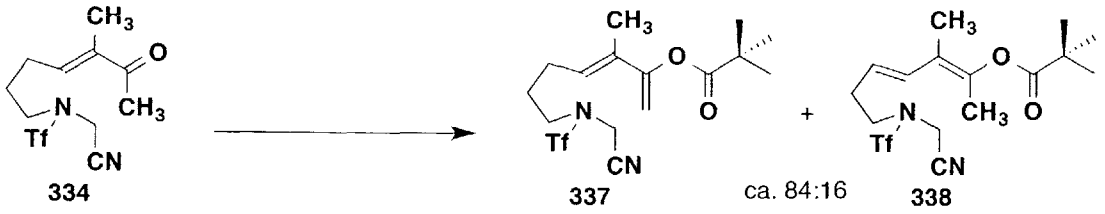
***N*-(Cyanomethyl)-*N*-(6-methyl-(*E*)-4-hepten-6-one)trifluoromethanesulfonamide (329).** A 250-mL, two-neck, round-bottomed flask equipped with glass stopper, and reflux condenser fitted with an argon through septum was charged with aldehyde **332** (2.72 g, 10.6 mmol, 1.0 equiv), 3-(Triphenylphosphoranylidene)butan-2-one (3.86 g, 11.6 mmol, 1.1 equiv), and 100 mL of THF. The reaction mixture was heated at reflux for 16 h, and then allowed to cool to rt and concentrated by rotary evaporation to give 7.72 g of an orange solid. A solution of this material in 40 mL of CH_2Cl_2 was concentrated onto 15 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 15-50% EtOAc-hexanes provided 2.99 g (91%) of **329** as a pale yellow oil: IR (neat): 2995, 2953, 2869, 1667, 1396, 1275, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (t, J = 7.3 Hz, 1 H), 4.32 (br s, 2 H), 3.56 (br s, 2 H), 2.28-2.33 (m, 2 H), 2.29 (s, 3 H), 1.89 (app quint, J = 7.5 Hz, 2 H), 1.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 139.9, 139.4, 119.8, 113.3, 49.2, 36.1, 26.7, 25.8, 25.7, 11.6; Anal. Calcd for $C_{11}H_{15}F_3N_2O_3S$: C, 42.30; H, 4.84; N, 8.97. Found: C, 42.35; H, 4.91; N, 8.91.

CH3
O
CH3
N
Tf
CN

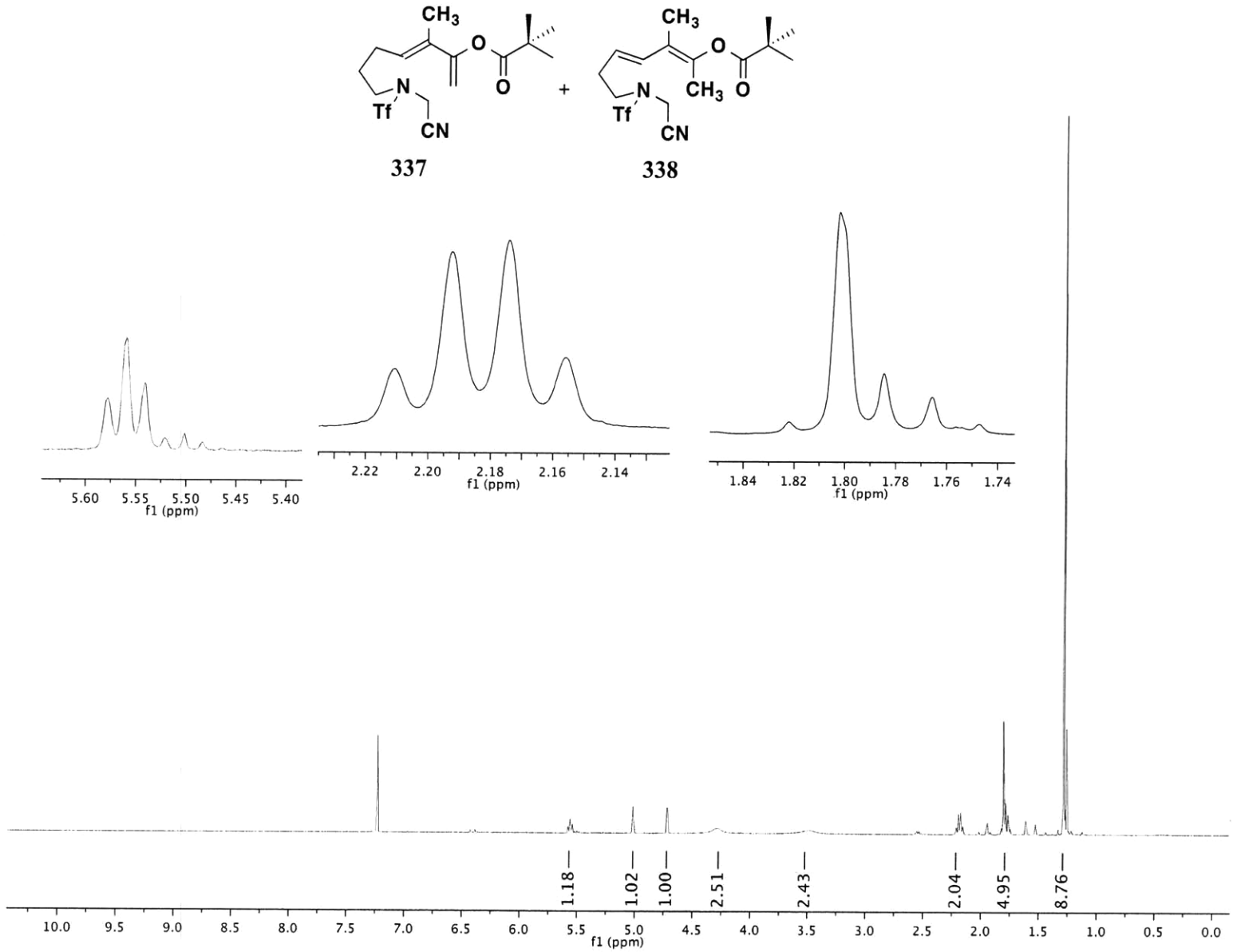
329

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

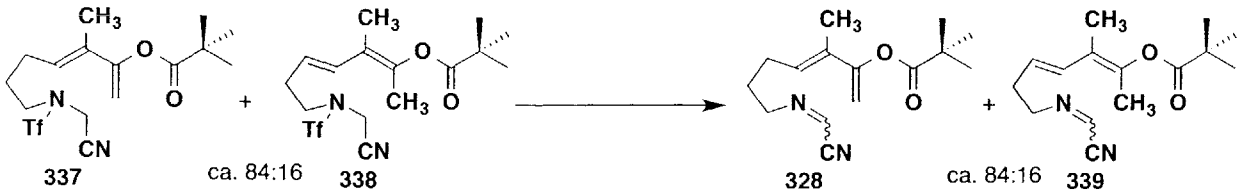

199.66
139.86
139.39
121.39
118.18
113.28
77.55
77.23
76.91
49.24
36.12
26.74
25.75
25.73
11.60
CH3
O
CH3
N
Tf
CN
329
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



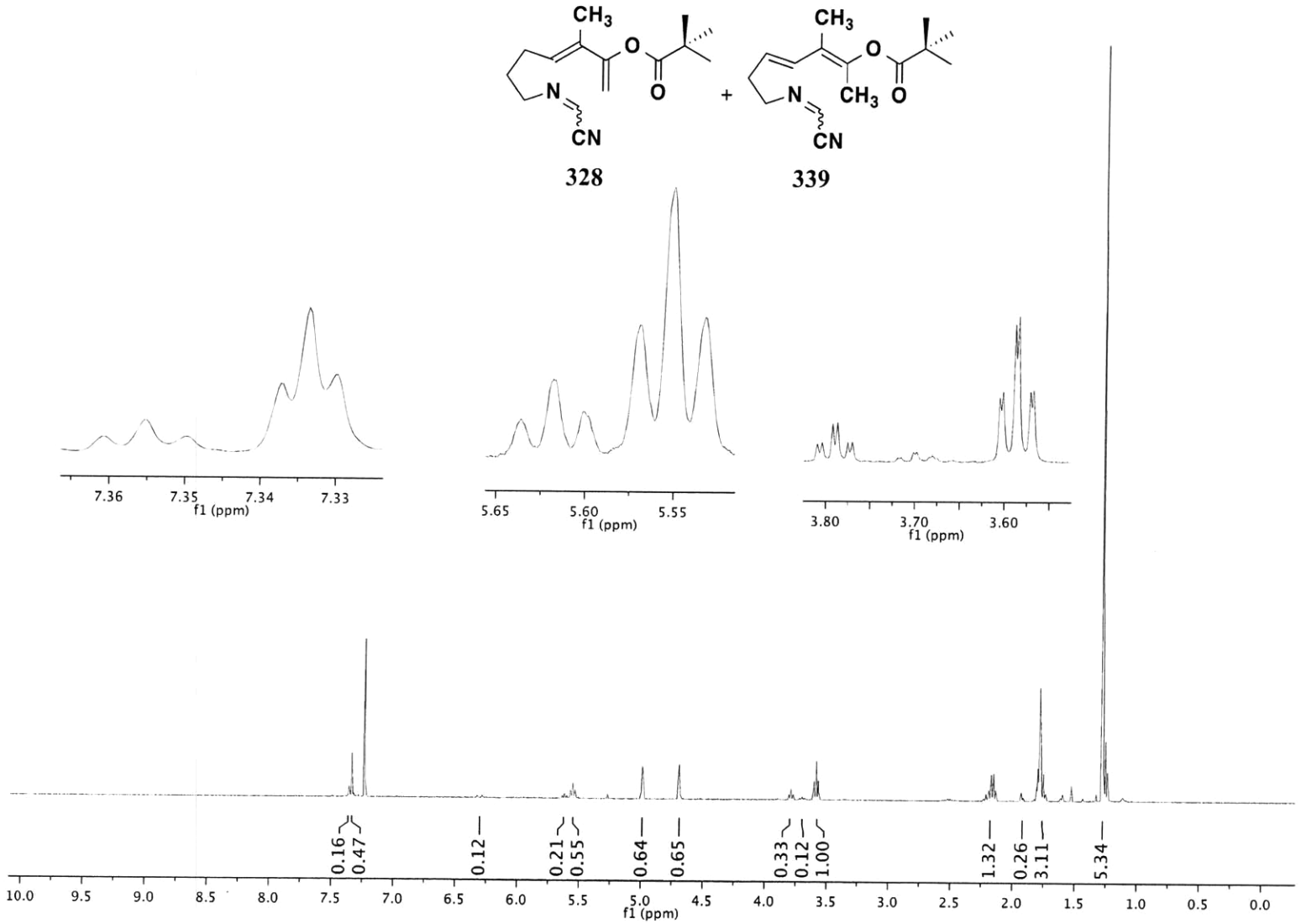
N-(Cyanomethyl)-N-(6-trimethyacetoxy)-5-methyl-(E)-4,6-heptadienyl)trifluoromethanesulfonamide (337). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with NaI (0.385 g, 2.57 mmol, 1.5 equiv), a solution of enone **334** (0.535 g, 1.71 mmol, 1.0 equiv) in 12 mL of CH_3CN, and trimethylacetyl chloride (0.317 mL, 0.310 g, 2.57 mmol). Et_3N (0.477 mL, 0.346 g, 3.42 mmol, 2.0 equiv) was added dropwise via syringe over 5 min, and the resulting mixture was stirred at rt in the dark for 24 h. The reaction mixture was then diluted with 25 mL of satd aq $NaHCO_3$ solution and 25 mL of CH_2Cl_2, and the aqueous layer was separated and extracted with three-25 mL portions of CH_2Cl_2. The combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.862 g of an orange oil. Column chromatography on 15 of silica gel (elution with 20% EtOAc-hexanes) provided 0.637 g (94%) of a 84:16 mixture of **337** and **338** as a yellow oil: For **337** IR (film): 2978, 2876, 1745, 1646, 1616, 1481, 1462, 1397, and 1267 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (t, J = 7.5 Hz, 1 H), 5.01 (s, 1 H), 4.72 (s, 2 H), 4.28 (br s, 1 H), 3.48 (br s, 2 H), 2.18 (app q, J = 7.3 Hz, 2 H), 1.75-182 (m, 2 H), 1.80 (s, 3 H), 1.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 154.4, 130.5, 125.6, 119.8 (q, J = 322 Hz), 113.6, 101.8, 49.4, 39.2, 36.2, 27.4, 27.2, 24.8, 13.5; Anal. Calcd for $C_{16}H_{23}F_3N_2O_4S$: C, 48.48; H, 5.85; N, 7.07. Found: C, 48.55; H, 5.81; N, 7.06.


CH3
O
O
N
Tf
CN
+
CH3
O
CH3 O
N
Tf
CN
337
338
5.60 5.55 5.50 5.45 5.40
f1 (ppm)
2.22 2.20 2.18 2.16 2.14
f1 (ppm)
1.84 1.82 1.80 1.78 1.76 1.74
f1 (ppm)
1.18
1.02
1.00
2.51
2.43
2.04
4.95
8.76
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

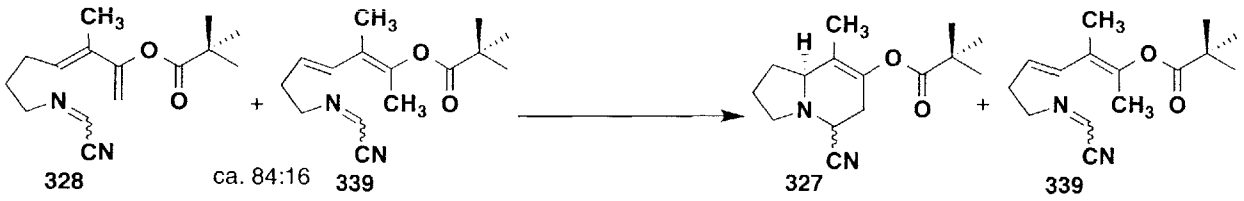
176.84
176.52
154.31
144.65
131.19
130.47
124.51
121.30
118.10
114.89
113.52
101.77
77.55
77.23
76.91
49.28
49.08
39.16
36.19
36.05
31.75
24.73
16.90
16.06
13.39
13.19
11.39
CH3
O
O
N
Tf
CN
+
CH3
O
CH3
O
N
Tf
CN
337
338
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



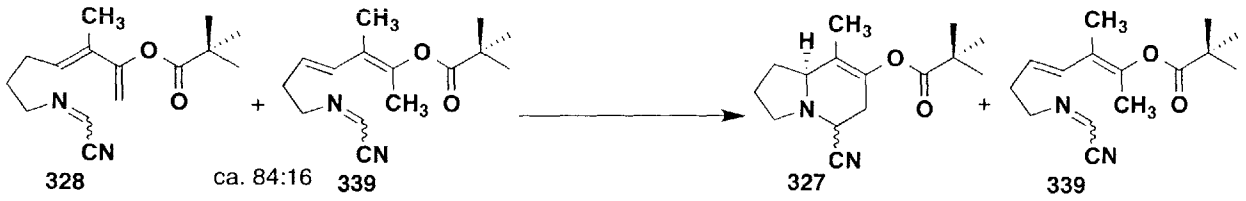
5-Methyl-6-trimethyacetoxy-(*E*)-4,6-heptadienyliminoacetonitrile (328). A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (2.094 g, 6.43 mmol, 4.0 equiv). A solution of triflamide (84:16 mixture of **337** and **338**, 0.637 g, 1.61 mmol, 1.0 equiv) in 12 mL of THF was then added in one portion, and the reaction mixture was heated at 50 °C for 2 h. The resulting mixture was allowed to cool to rt and then diluted with 25 mL of water. The aqueous layer was separated and extracted with three 20-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.375 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 20% EtOAc-hexanes containing 1% Et_3N) afforded 0.345 g (82%) of **328** and **339** (75:25 mixture of *E* and *Z* imine isomers by ^1H NMR analysis, ca. 84:16 ratio of **328** to **339**) as a yellow oil: IR (film): 2975, 2873, 1747, 1645, 1618, 1480, 1416, 1368, and 1263 cm^{-1}; for *Z* isomer **328**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 2.2 Hz, 1 H), 5.62 (app t, J = 6.9 Hz, 1 H), 4.99 (s, 1 H), 4.69 (s, 1 H), 3.79 (td, J = 6.8, 2.2 Hz, 2 H), 2.13-2.26 (m, 2 H), 1.73-1.80 (m, 2 H), 1.78 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 154.6, 136.4, 131.8, 127.0, 114.6, 101.5, 59.3, 39.3, 29.7, 27.2, 25.9, 13.5; for *E* isomer **328**: ^1H NMR (400 MHz, $CDCl_3$) 67.33 (t, J = 1.4 Hz, 1 H), 5.55 (app t, J = 7.3 Hz, 1 H), 4.99 (s, 1 H), 4.69 (s, 1 H), 3.59 (td, J = 6.8, 1.4 Hz, 2 H), 2.13-2.26 (m, 2 H), 1.73-1.80 (m, 2 H), 1.78 (s, 3 H), 1.26 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 154.6, 136.4, 129.9, 126.8, 114.6, 101.5, 62.2, 39.3, 29.5, 27.4, 25.5, 13.5; Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70.


CH3
O
O
N
CN
328
+
CH3
O
CH3
O
N
CN
339
7.36
7.35
7.34
7.33
f1 (ppm)
5.65
5.60
5.55
f1 (ppm)
3.80
3.70
3.60
f1 (ppm)
0.16
0.47
0.12
0.21
0.55
0.64
0.65
0.33
0.12
1.00
1.32
0.26
3.11
5.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

176.91
154.58
136.37
131.79
129.91
127.05
126.84
114.60
101.52
101.46
77.55
77.23
76.91
62.23
59.33
39.27
29.51
27.43
27.30
25.99
25.54
13.54
CH3
O
O
N
CN
XX
+
CH3
O
CH3
O
N
CN
XX
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

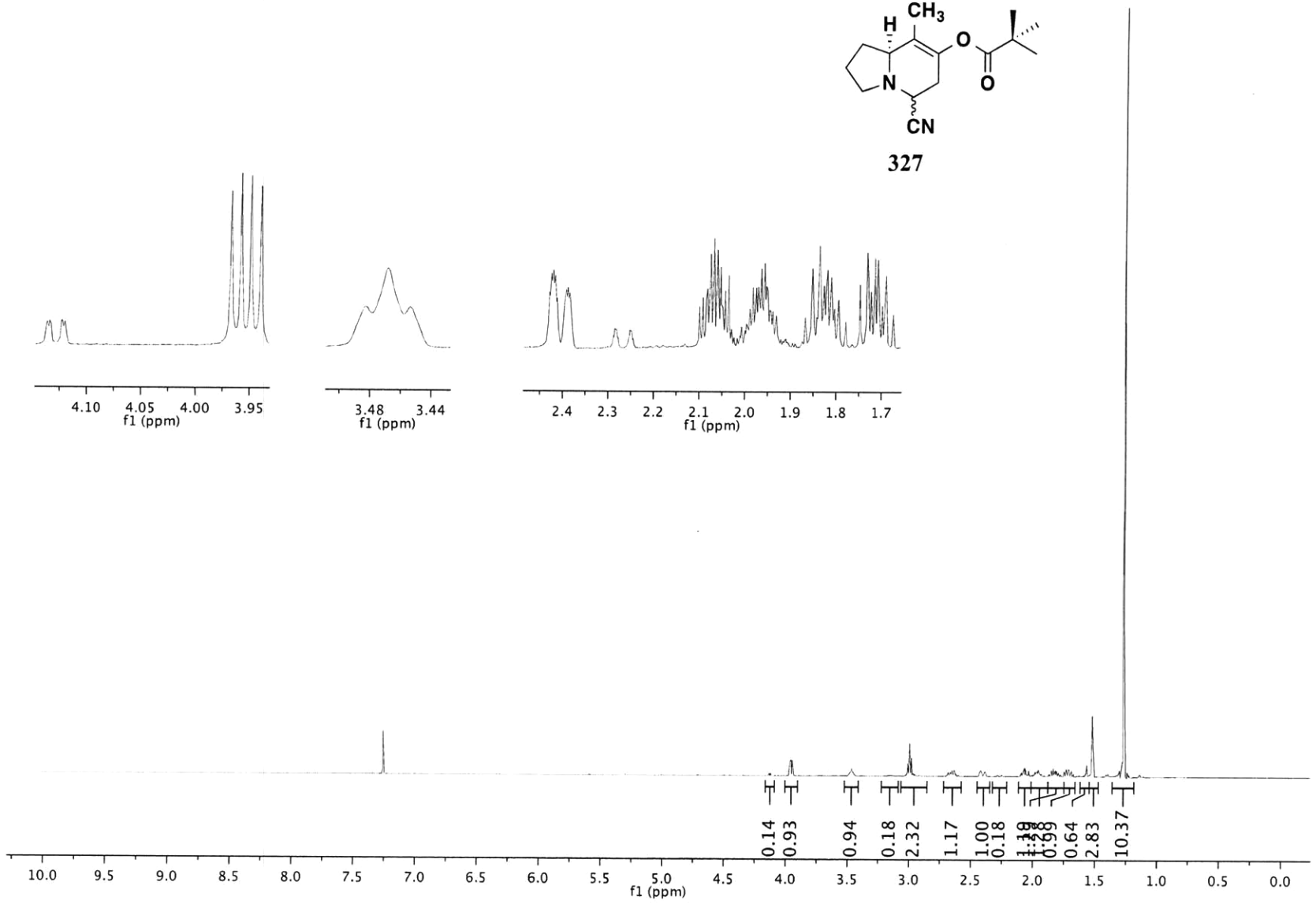


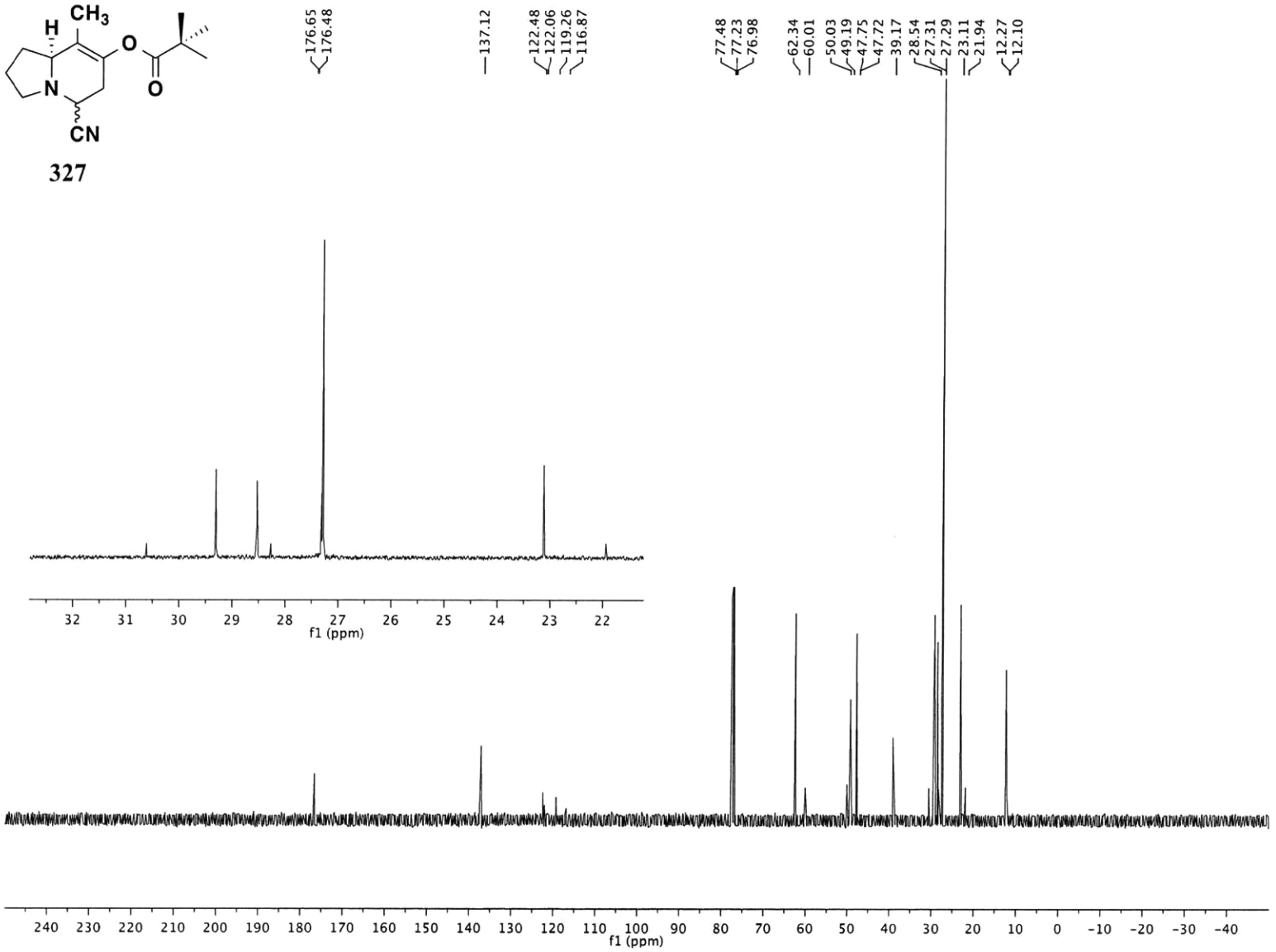
8-Methyl-*cis*-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (327a) and **8-Methyl-*trans*-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (327b).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **328** (0.345 g of a 84:16 mixture of dienes, 1.32 mmol, 1.0 equiv), ca. 0.100 g of powdered 4 Å molecular sieves, and 100 mL of CH_2Cl_2. The solution was cooled at 0 °C while methanesulfonic acid (0.73 M in CH_2Cl_2, 1.81 mL, 0.127 g, 1.32 mmol, 1.0 equiv) was added dropwise via syringe over 3 min. The reaction mixture was stirred at 0 °C for 2 h and then diluted with 20 mL of satd aq $NaHCO_3$. The aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.355 g of an orange oil. Purification by column chromatography on 20 g of silica gel (elution with 25% EtOAc-hexanes containing 1% Et_3N) afforded 0.245 g (55% overall from **329**) of **327a** and **327b** (84:16 mixture by ^1H NMR analysis) as an orange oil: IR (CH_2Cl_2): 2974, 2874, 2817, 1743, 1703, 1481, 1462, 1397, 1368, 1328, 1277 cm^{-1}; For **327a**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.10 (d, J = 5.7 Hz, 1 H), 3.13 (br s, 1 H), 2.87- 2.98 (m, 2 H), 2.57-2.67 (m, 1H), 2.37 (dm, J = 16.1 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 137.1, 122.0, 116.8, 60.0, 50.0, 47.7, 39.1, 30.6, 28.5, 27.3, 21.9, 12.1: For **327b**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.02 (dd, J = 9.2, 4.6 Hz, 1 H), 3.44 (t, J = 7.1 Hz, 1 H), 2.87-2.98 (m, 2 H), 2.57-2.67 (m, 1 H), 2.24 (d, J = 16.0 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 137.1, 122.5, 119.3, 62.3, 49.1, 47.7, 39.1, 29.3, 28.5, 27.3, 23.1, 12.2; Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70.



8-Methyl-*cis*-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (327a) and **8-Methyl-*trans*-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (327b).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **328** (0.949 g of a 84:16 mixture of dienes, 3.62 mmol, 1.0 equiv), ca. 0.300 g of powdered 4 Å molecular sieves, and 26 mL of CH_2Cl_2. The solution was cooled at -40 °C while (*R*)-TRIP (2.72 g, 3.62 mmol, 1.0 equiv) was added as a solution in 10 mL of CH_2Cl_2 dropwise via cannula over 10 min. The reaction mixture was allowed to warm to -25°C and was stirred -25 °C for 72 h and then diluted with 30 mL of 1 M NaOH solution. The aqueous layer was separated and extracted with three 30-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow semi-solid. Purification by column chromatography on 60 g of silica gel (gradient elution with 10-20% EtOAc-hexanes containing 1% Et_3N) afforded 0.647 g (55% overall from **329**) of **327a** and **327b** (84:16 mixture by ^1H NMR analysis) (70:30 er determined by making the (R)-BNPA salt of the product) as an orange oil: IR (CH_2Cl_2): 2974, 2874, 2817, 1743, 1703, 1481, 1462, 1397, 1368, 1328, 1277 cm^{-1}; For **327a**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.10 (d, *J* = 5.7 Hz, 1 H), 3.13 (br s, 1 H), 2.87- 2.98 (m, 2 H), 2.57-2.67 (m, 1H), 2.37 (dm, *J* = 16.1 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 137.1, 122.0, 116.8, 60.0, 50.0, 47.7, 39.1, 30.6, 28.5, 27.3, 21.9, 12.1: For **327b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (dd, *J* = 9.2, 4.6 Hz, 1 H), 3.44 (t, *J* = 7.1 Hz, 1 H), 2.87-2.98 (m, 2 H), 2.57-2.67 (m, 1 H), 2.24 (d, *J* = 16.0 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 137.1, 122.5, 119.3, 62.3, 49.1, 47.7, 39.1, 29.3, 28.5, 27.3, 23.1, 12.2; Anal. Calcd for

$C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70. $[\alpha]^{25}_D$ -24.0(*c* 1.0, $CHCl_3$)


CH3
H
O
N
O
CN
327
4.10
4.05
4.00
3.95
f1 (ppm)
3.48
3.44
f1 (ppm)
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
f1 (ppm)
0.14
0.93
0.94
0.18
2.32
1.17
1.00
0.18
0.99
0.64
2.83
10.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CH3
H
O
N
O
CN
327
176.65
176.48
137.12
122.48
122.06
119.26
116.87
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77.23
76.98
62.34
60.01
50.03
49.19
47.75
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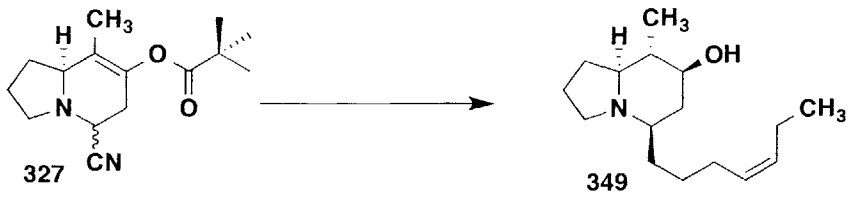
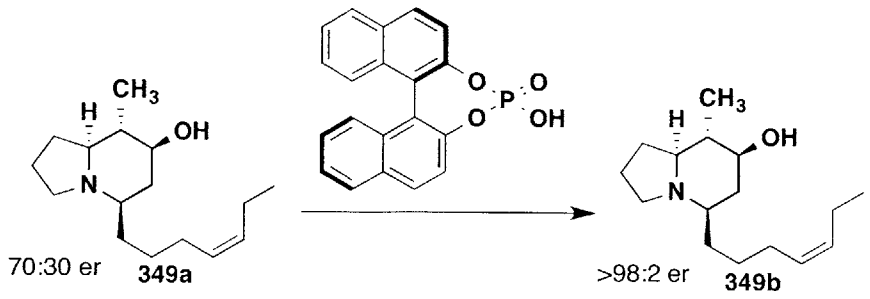
21.94
12.27
12.10
f1 (ppm)
f1 (ppm)



(5α, 8β, 9β)-5-(4-Heptene)-8-methyl-7-indolizidinol (349). A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (1.68 mL, 1.25 g, 7.74 mmol, 2.5 equiv) and 12 mL of THF. The solution was cooled at 0 °C while BuLi (2.60 M in hexane, 2.98 mL, 7.74 mmol, 2.5 equiv) was added dropwise via syringe over 15 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **327** (0.816 g, 3.10 mmol, 1.0 equiv) in 3 mL of THF was added dropwise via cannula over 2 min. The resulting solution was stirred at -78 °C for 2 h, and then a solution of 1-bromo-4-heptene (0.604 g, 3.10 mmol, 1.0 equiv) in 1 mL of THF was added rapidly cannula. The reaction mixture was stirred at 0 °C for 2 h, and then diluted with 30 mL of ether and 30 mL of water. The aqueous layer was extracted with three 30-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 2.23 g of an orange oil that was used immediately in the next step without further purification.

Approximately 100 mL of NH_3 was condensed at -78 °C into a 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and a Dewar condenser fitted with a rubber septum and argon inlet needle. Sodium metal (0.712 g, 31.0 mmol, 10 equiv) was added and the resulting blue solution was stirred at -78 °C for 1.5 h. A solution of the amino nitrile prepared above in 12 mL of THF was then added over ca. 2 min via cannula, and the resulting mixture was stirred at -78 °C for 30 min. Sodium metal (1.42 g, 62.0 mmol, 20 equiv) was added followed by the addition of EtOH (1.05 mL, 1.43 g, 31.0 mmol, 10 equiv) via syringe, and the resulting mixture was stirred at -78 °C for 45 min. MeOH (25 mL) was next added dropwise via syringe over 15 min and the

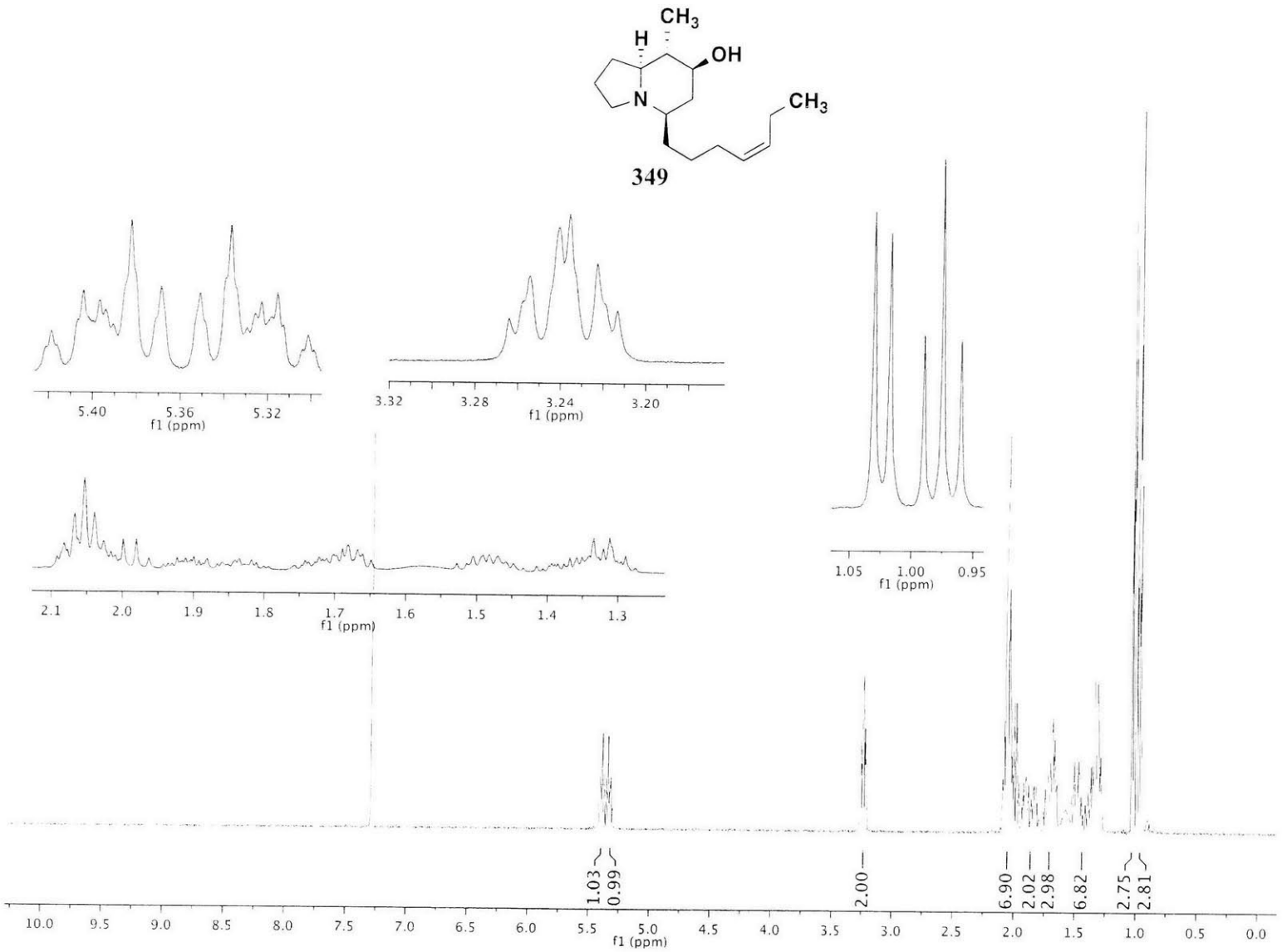
reaction mixture was stirred for 1 h at -78 °C, and then the reaction mixture was allowed to warm to rt over 1 h while the NH_3 evaporated through an outlet needle and the resulting mixture was poured into 50 mL of H_2O and extracted with four 40-mL portions of CH_2Cl_2. The combined organic layers were washed with 40 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.821 g of an orange oil. Purification by column chromatography on 35 g of silica gel (gradient elution with 30%-100% EtOAc-hexanes) afforded 0.441 g (57%) of **349** as a light yellow oil: IR (thin film) 3377, 2960, 2872, 2782, 1458, 1374, 1050, and 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28-5.40 (m, 2 H), 3.19-3.25 (m, 2 H), 1.95-2.08 (m, 7 H), 1.79-1.93 (m, 3 H), 1.64-1.74 (m, 3 H), 1.24-1.55 (m, 6 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.96 (t, J = 8.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.1, 128.9, 75.2, 69.3, 61.0, 51.4, 44.5, 40.5, 34.0, 28.9, 27.4, 25.9, 21.3, 20.7, 14.6, 14.5; Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.52; H, 11.62; N, 5.52. $[\alpha]^{24}_D$ -17.8 (*c* 1.0, $CHCl_3$)

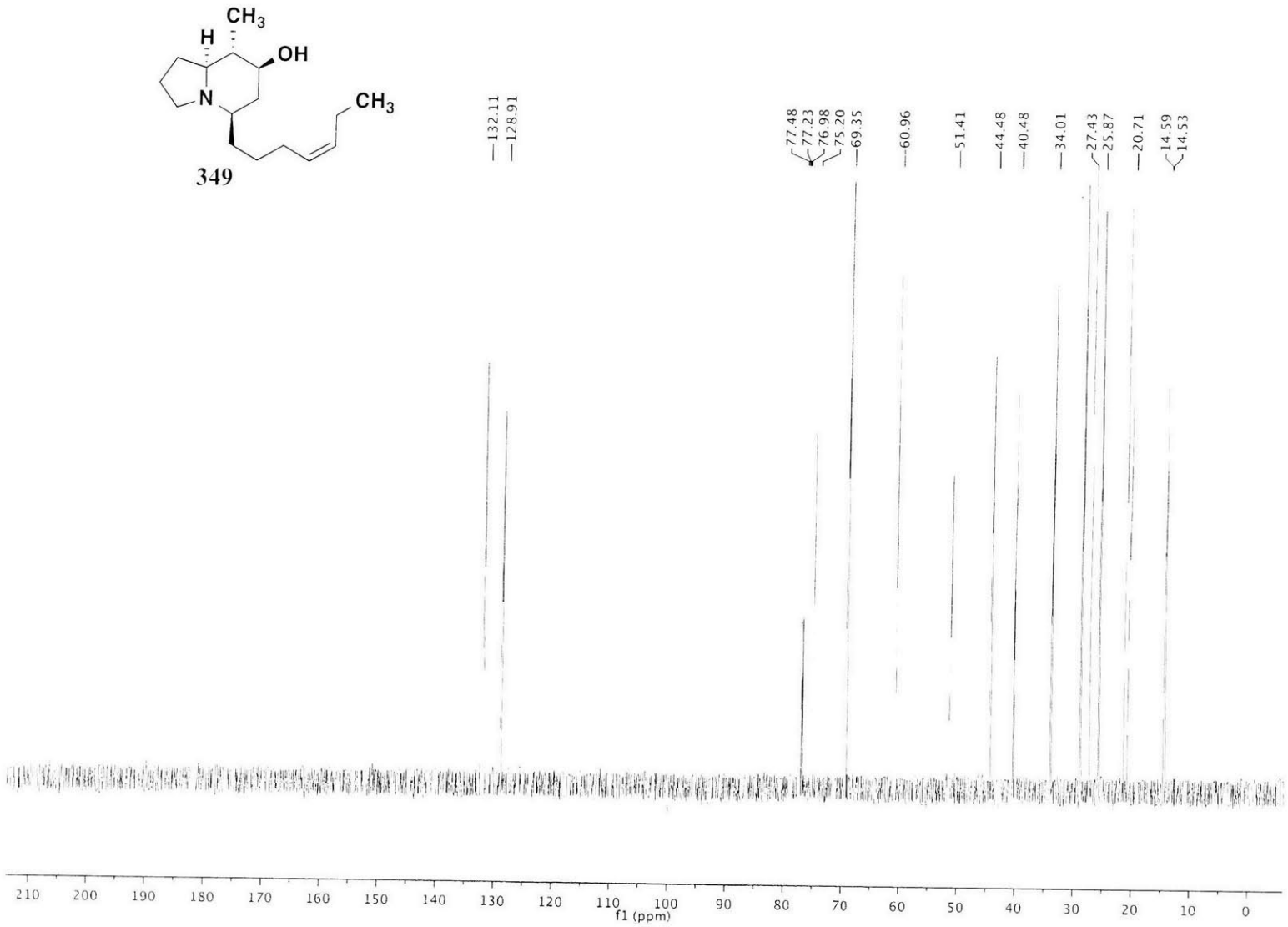


(5*R*, 7*S*, 8*R*, 9*S*)-5-(4-heptene)-8-methyl-7-indolizidinol (349b). A 100-mL, round-bottomed flask was charged with indolizidine **349a** (0.436 g, 1.74 mmol, 1.0 equiv) in 50 mL of MeOH. (*R*)-(-)-1,1'-Binaphthyl-2,2'-diylphosphoric acid (0.606 g 1.74 mmol, 1.0 equiv) was added in one portion and the resulting mixture was stirred at rt for 5 min until all of the solids had dissolved. The resulting solution was concentrated to afford a white solid. This material was dissolved in 16 mL of hot MeOH (60 °C) and the solution was allowed to cool to 0 °C over 3 h, allowed to stand at 0 °C for 1 h, and then stored at -25 °C for 18 h. The resulting white needles were collected by suction filtration on a Buchner funnel and washed with 5 mL of cold MeOH to afford 0.483 g of white crystals (>98:2 er by ^{1}H NMR analysis). The filtrate was concentrated to provide an off-white solid that was dissolved in 8 mL of hot MeOH (60 °C). The solution was allowed to cool to rt over 2 h, allowed to stand at rt for 1 h, and then stored at -25 °C for 16 h. The resulting white needles were collected by suction filtration on a Buchner funnel and washed with 2 mL of cold MeOH to afford 0.113 g of white crystals (>98:2 er by ^{1}H NMR analysis).

The two crops of crystals were dissolved in 20 mL of CH_2Cl_2 and 20 mL of 1 M aq NaOH in a 100-mL recovery flask and stirred vigorously for 10 min. The resulting heterogeneous mixture was filtered through a 1-inch pad of Celite in a Buchner funnel with the aid of 50 mL of CH_2Cl_2 and 20 mL of 1 M aq NaOH solution. The aqueous phase of the filtrate was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic phases were washed with 25 mL of satd aq NaCl

solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.244 g of a colorless oil with spectral data consistent with that reported previously. $[\alpha]^{24}_D$ -78.1(*c* 1.0, $CHCl_3$)


CH3
H
OH
N
CH3
349
5.40
5.36
5.32
f1 (ppm)
3.32
3.28
3.24
3.20
f1 (ppm)
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
f1 (ppm)
1.05
1.00
0.95
f1 (ppm)
1.03
0.99
2.00
6.90
2.02
2.98
6.82
2.75
2.81
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CH3
H
OH
N
CH3
349
132.11
128.91
77.48
77.23
76.98
75.20
69.35
60.96
51.41
44.48
40.48
34.01
27.43
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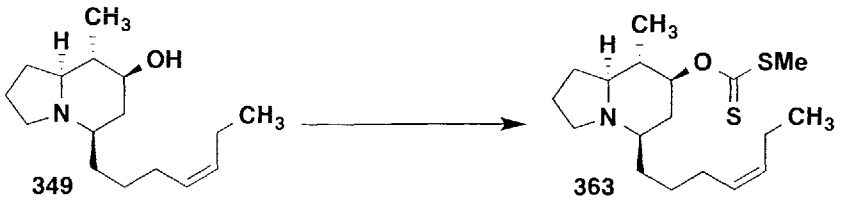
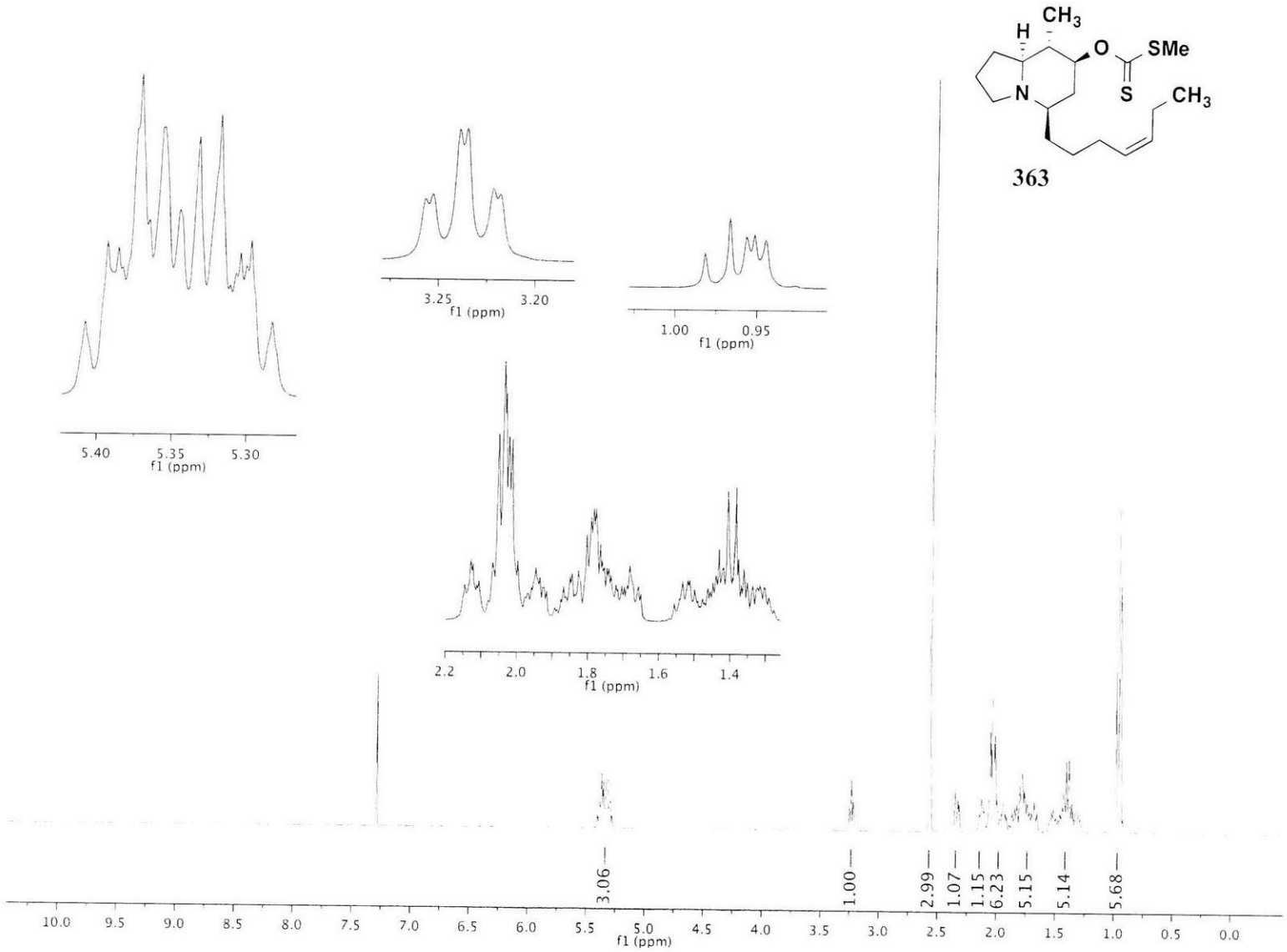
20.71
14.59
14.53
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



(5*R*, 7*S*, 8*R*, 9*S*)-5-(Hept-4-enyl)-8-methyl-indolizin-7-ol-S-methyl dithiocarbonate (363). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and reflux condenser fitted with a rubber septum and argon inlet needle was charged with NaH (0.116 g, 40% mineral oil dispersion, 2.91 mmol, 3.0 equiv) and 5 mL of THF. A solution of indolizidine **349** (0.244 g, 0.970 mmol, 1.0 equiv) and imidazole (0.007 g, 0.1 mmol, 0.1 equiv) in 5 mL of THF was added dropwise via cannula over 5 min, and the resulting mixture was stirred at rt for 2 h and then CS_2 (0.23 mL, 0.37 g, 4.85 mmol, 5.0 equiv) was added in one portion via syringe. The rubber septum was replaced with a glass stopper and the reaction mixture was heated at reflux for 1 h, allowed to cool to rt, and MeI (0.09 mL, 0.206 g, 1.46 mmol, 1.5 equiv) was added in one portion via syringe through the condenser. The resulting mixture was stirred at rt for 45 min and then diluted with 25 mL of water and 25 mL of CH_2Cl_2. The aqueous layer was separated and extracted with two 25-mL portions of CH_2Cl_2, and the combined organic layers were washed with 25 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.375 g of an orange oil. Purification by column chromatography on 35 g of SiO_2 (elution with 20% EtOAc-hexanes) afforded 0.228 g (69%) of **363** as a yellow oil: $[\alpha]^{24}_D$ +22 (*c* 1.0, $CHCl_3$); IR (thin film): 2962, 2932, 2785, 1710, 1459, 1223, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27-5.40 (m, 3 H), 3.23 (td, *J* = 9.0, 2.0 Hz, 1 H), 2.56 (s, 3 H), 2.31-2.35 (m, 1 H), 2.09-2.14 (m, 1 H), 1.91-2.07 (m, 6 H), 1.64-1.88 (m, 5 H), 1.26-1.55 (m, 5 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 0.94 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 132.2, 128.8, 87.0, 69.0, 60.3, 51.3, 41.9, 35.5, 34.1, 29.0, 27.4, 25.6, 21.3, 20.7, 19.0, 14.62, 14.57; Anal. Calcd for $C_{18}H_{31}NOS_2$: C, 63.29; H, 9.15; N, 4.10. Found: C, 63.23, H, 9.36, N, 4.10.


CH3
H
O
SMe
N
S
CH3
363
5.40
5.35
5.30
f1 (ppm)
3.25
3.20
f1 (ppm)
1.00
0.95
f1 (ppm)
2.2
2.0
1.8
1.6
1.4
f1 (ppm)
3.06
1.00
2.99
1.07
1.15
6.23
5.15
5.14
5.68
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

216.21
CH3
H
O
SMe
N
S
CH3
132.20
128.84
87.03
77.48
77.23
76.98
69.02
60.29
51.30
41.91
35.53
34.06
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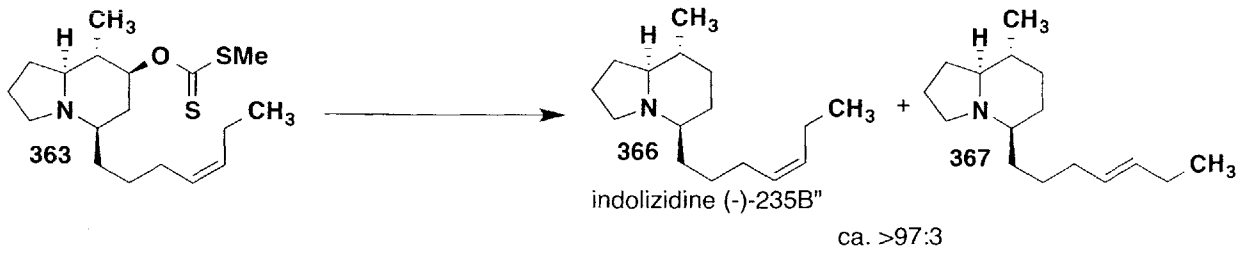
f1 (ppm)

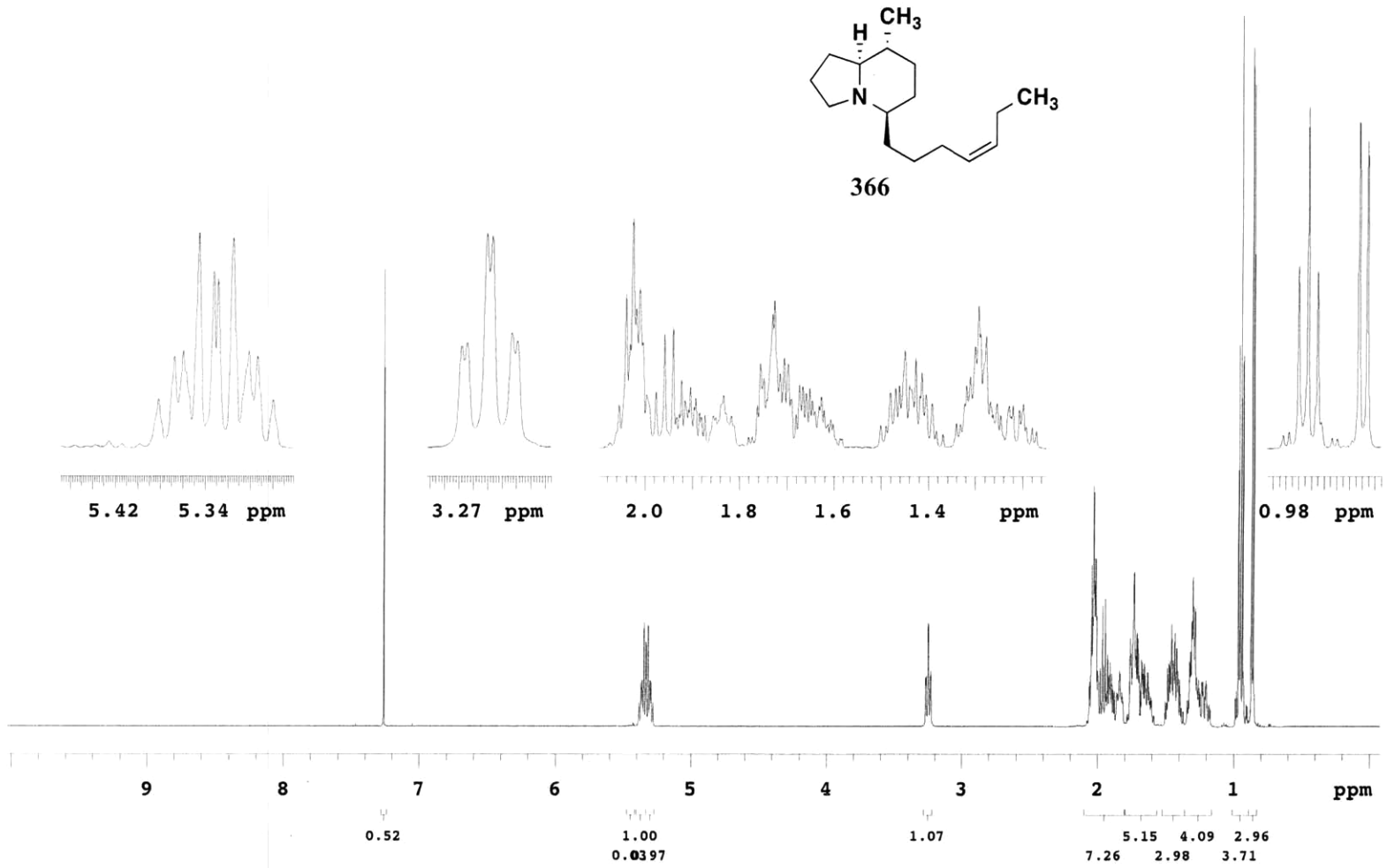
363



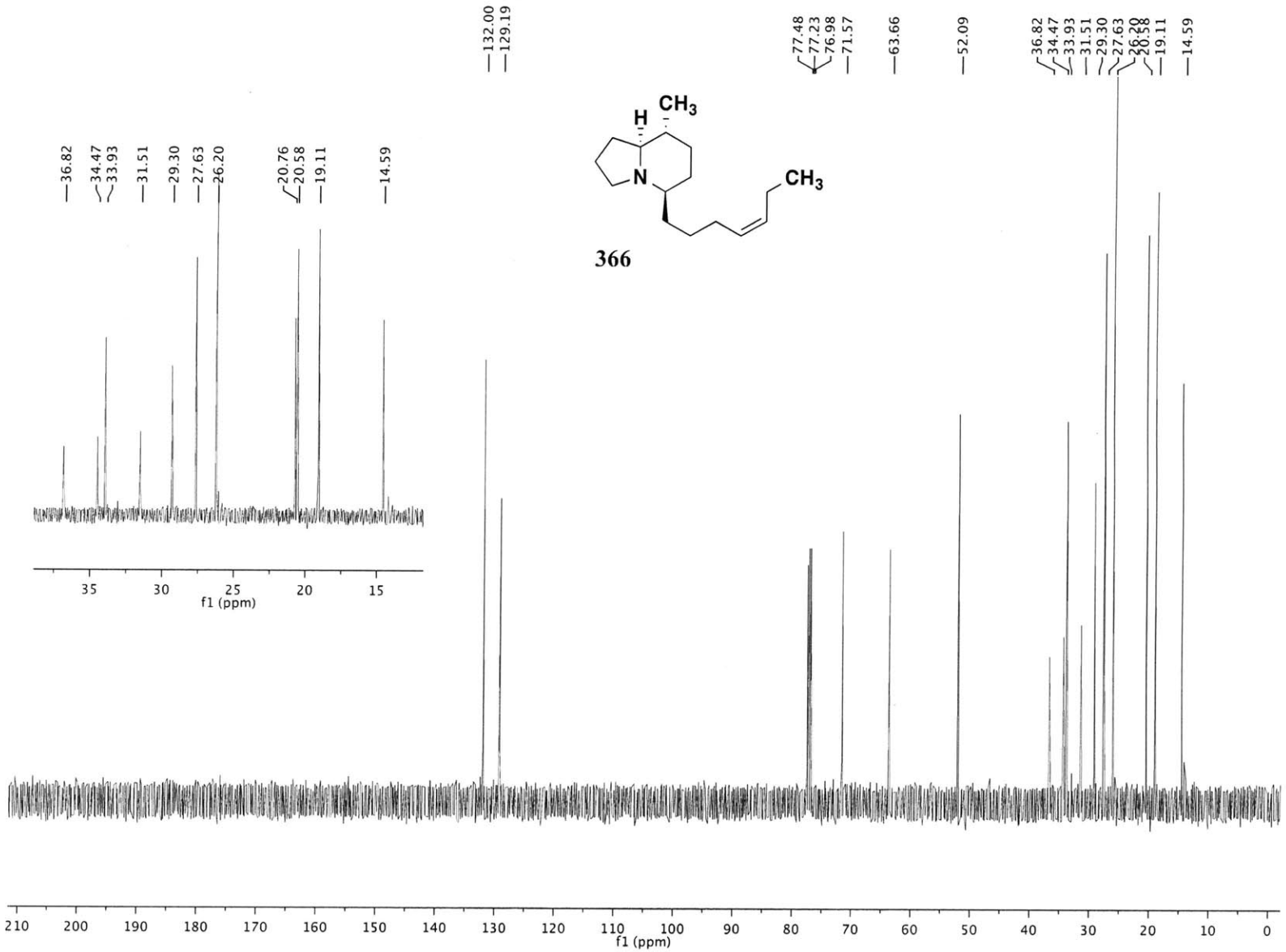
(5*R*, 8*R*, 9*S*)-5-(Hept-4-enyl)-8-methyl-indolizidine 235B" (366).[15] A 50-mL, two-necked round-bottomed flask equipped with a rubber septum and reflux condenser fitted with a rubber septum and argon inlet needle was charged with AIBN (0.010 g, 0.065 mmol, 0.1 equiv) and a solution of Cy_3SnH (0.482 g, 1.31 mmol, 2.0 equiv) in 10 mL of toluene. The septum was replaced with a glass stopper, and the reaction mixture was heated at reflux while a solution of **363** (0.223 mg, 0.653 mmol, 1.0 equiv) in 10 mL of 1-hexene and 1 mL of toluene was added via cannula through the condenser over 2 min. The resulting mixture was stirred at reflux for 10 min, cooled to rt, and then concentrated to an oil that was diluted with 15 mL of hexanes and 15 mL of 1 N HCl solution. The aqueous layer was extracted with three 10-mL portions of hexanes, and then diluted with 15 mL of $CHCl_3$ and 20 mL of 1 N NaOH solution. The aqueous layer was separated and extracted with three 15-mL portions of $CHCl_3$ and the combined chloroform layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.132 g of a yellow oil. Purification by column chromatography on 15 g of SiO_2 (elution with 1% MeOH-$CHCl_3$ containing 0.3% NH_4OH) afforded 0.119 g (77%) (-)-indolizidine 235B" and **366** (>97:3 mixture by ^1H NMR analysis) as a colorless oil: $[\alpha]^{24}_D$ -90 (c 1.0, MeOH); IR (thin film) 2962, 2873, 2777, 1457, 1375, 1133 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27-5.38 (m, 2 H), 3.29 (br s, 1 H), 1.85-2.05 (m, 7 H), 1.70-1.80 (m, 3 H), 1.60-1.70 (m, 2 H), 1.20-1.58 (7 H), 0.91-1.00 (m, 1 H), 0.94 (t, J = 7.5 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.0, 129.2, 71.6, 63.7, 52.1, 36.8, 34.5, 33.9, 31.5, 29.3, 27.6, 26.2, 20.8 20.6,

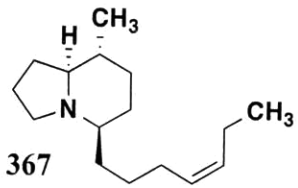
[15] Indolizidine (+)-235B" was prepared following a similar procedure using (-)-(5*S*, 7*R*, 8*S*, 9*R*)-5-(Hept-4-enyl)-8-methyl-indolizin-7-ol-S-methyl dithiocarbonate (**363**). Spectra of (+)-235B" are identical to the spectra reported for (-)-235B". $[\alpha]^{24}_D$ +89 (*c* 1.0, MeOH).

19.1, 14.6; Anal. Calcd for $C_{16}H_{29}N$: C, 81.63; H, 12.42; N, 5.95. Found: C, 81.73; H, 12.43; N, 5.97. $[\alpha]^{24}_{D}$ -90.0 (*c* 1.0, MeOH)


CH3
H
N
CH3
5.42
5.34 ppm
3.27 ppm
2.0
1.8
1.6
1.4 ppm
0.98 ppm
9
8
7
6
5
4
3
2
1
ppm
0.52
1.00
0.0397
1.07
5.15
4.09
2.96
7.26
2.98
3.71

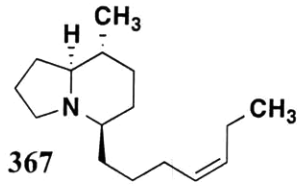
366


132.00
129.19
77.48
77.23
76.98
71.57
63.66
52.09
36.82
34.47
33.93
31.51
29.30
27.63
26.20
20.76
20.58
19.11
14.59
CH3
H
N
CH3
366
f1 (ppm)



367

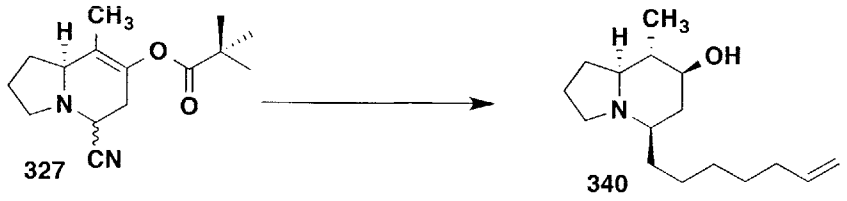
gCOSY


H
CH3
N
CH3

367

gCOSY

F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
F1 (ppm)



(5α,8β,9β)-5-(6-heptene)-8-methyl-7-indolizidinol (340). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (0.40 mL, 0.308 g, 1.91 mmol, 2.5 equiv) and 3.5 mL of THF. The solution was cooled at 0 °C while a solution of *n*-BuLi (0.81 mL, 2.35 M in hexane, 1.91 mmol, 2.5 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **327** (0.200 g, 0.76 mmol, 1.0 equiv) in 1 mL of THF was added dropwise via cannula over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then 7-bromoheptene (0.13 mL, 0.149 g, 0.84 mmol, 1.1 equiv) was added rapidly via syringe. The reaction mixture was stirred at 0 °C for 2 h, and then diluted with 15 mL of ether and 15 mL of water. The aqueous layer was extracted with two 15-mL portions of ether, and the combined organic layers were washed with 15 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 450 g of an orange oil that was used immediately in the next step without further purification.

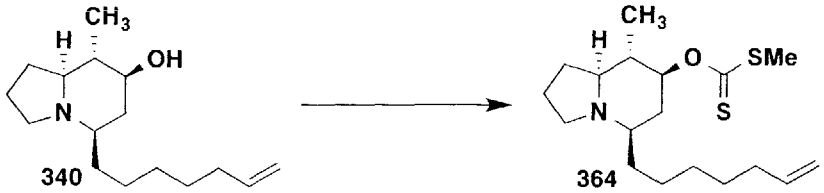
Approximately 25 mL of NH_3 was condensed at -78 °C into a 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and a Dewar condenser fitted with a rubber septum and argon inlet needle. Sodium metal (0.175 g, 7.60 mmol, 10 equiv) was added and the resulting blue solution was stirred at -78 °C for 45 min. A solution of the amino nitrile prepared above in 5 mL of THF was then added over ca. 2 min via cannula, and the resulting mixture was stirred at -78 °C for 30 min. Sodium metal (0.175 g, 7.60 mmol, 10 equiv) was added followed by the addition of EtOH (0.26 mL, 0.35 g, 7.6 mmol, 10 equiv) via syringe, and the resulting mixture was stirred at -78 °C for 45 min. MeOH (8 mL) was next added dropwise via syringe over 15 min and the reaction mixture was stirred for 45 min at -78 °C, and then the reaction mixture was allowed to warm

to rt over 1.5 h while the NH_3 evaporated through an outlet needle and the resulting mixture was poured into 20 mL of H_2O and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 25 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.209 g of an orange oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 4-10% MeOH/CH_2Cl_2) afforded 0.090 g (47%) of **340**[16] (containing ca. 8% of the saturated substituent) as a white solid: mp: 51-53 °C; IR (KBr): 2964, 2920, 2859, 2792, 1642, 1467, 1375 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 4.93 (dm, J = 17.1 Hz, 1 H), 4.87 (dm, J = 10.2 Hz, 1 H), 3.10-3.17 (m, 2 H), 1.55-2.00 (m, 10 H), 1.19-1.45 (m, 11 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 114.4, 75.2, 69.4, 61.0, 51.4, 44.5, 40.5, 34.4, 33.9, 29.6, 29.0, 28.9, 25.6, 21.3, 14.6; Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.38; H, 11.63; N, 5.57.

[16] $[\alpha]^{24}_D$ -75.9 (*c* 1.0, $CHCl_3$) after resolution

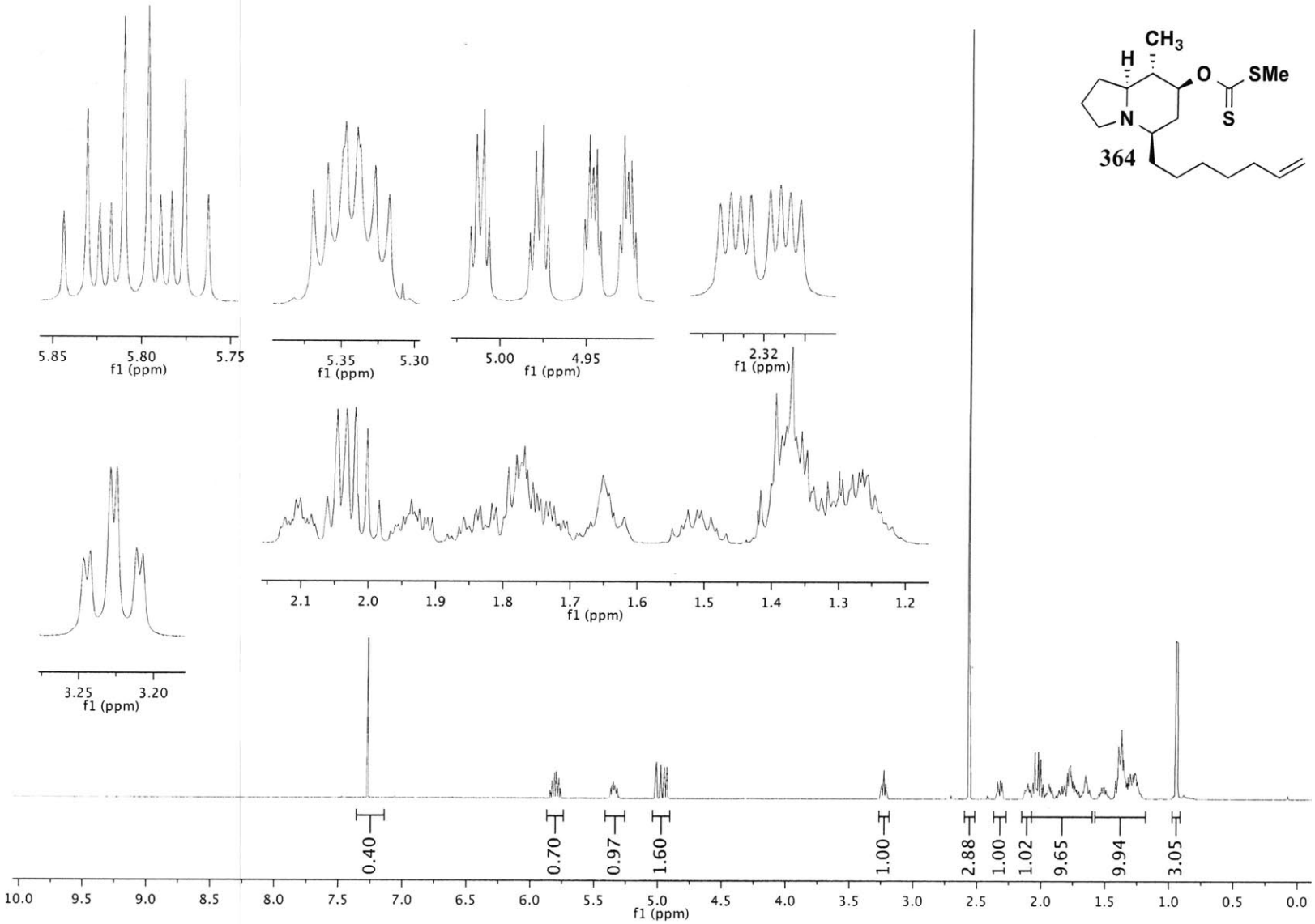
CH3
H
OH
N
340
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

139.19
114.40
77.55
77.23
76.91
75.19
69.34
61.02
51.42
44.49
40.45
34.38
33.88
28.86
25.59
21.32
14.61
H
CH3
OH
N
340
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

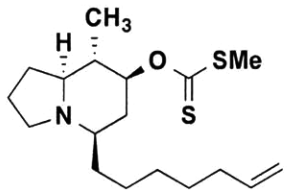


(5R,8R,9S)-5-(6-heptene)-8-methyl indolizindin-7-yl S-methyl dithiocarbonate (364). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and reflux condenser fitted with a rubber septum and argon inlet needle was charged with NaH (0.024 g, 40% mineral oil dispersion, 0.6 mmol, 3.0 equiv). A solution of indolizidine **340** (0.51 g, 0.20 mmol, 1.0 equiv) and imidazole (0.001 g, 0.1 mmol, 0.1 equiv) in 1.5 mL of THF was added dropwise via cannula over 1 min, and the resulting mixture was stirred at 50 °C for 2.5 h and then CS_2 (0.047 mL, 0.076 g, 1.0 mmol, 5.0 equiv) was added in one portion via syringe. The rubber septum was replaced with a glass stopper and the reaction mixture was heated at reflux for 30 min, allowed to cool to rt, and MeI (0.018 mL, 0.042 g, 0.30 mmol, 1.5 equiv) was added in one portion via syringe through the condenser. The resulting mixture was stirred at rt for 30 min and then diluted with 10 mL of water and 10 mL of CH_2Cl_2. The aqueous layer was separated and extracted with two 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 15 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.088 g of an orange oil. Purification by column chromatography on 8 g of SiO_2 (elution with 10% EtOAc-hexanes) afforded 0.057 g (84%) of **364** as a yellow oil: IR (neat): 3075, 2929, 2785, 1641, 1224, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.2, 10.3, 6.7 Hz, 1 H), 5.34 (ddd, J = 11.0, 10.2, 4.9 Hz, 1 H), 5.00 (ddt, J = 17.1, 2.1, 1.7 Hz, 1 H), 4.94 (ddt, J = 10.1, 2.1, 1.2 Hz, 1 H), 3.23 (ddd, J = 8.7, 8.7, 2.1 Hz, 1 H), 2.56 (s, 3 H), 2.32 (ddd, J = 12.2, 5.0, 2.6 Hz, 1 H), 2.11 (m, 1 H), 2.04 (m, 2 H), 2.00 (m, 1 H), 1.93 (m, 1 H), 1.69-1.88 (m, 4 H), 1.65 (m, 2 H), 1.51 (m, 1 H), 1.22-1.42 (m, 7 H), 0.94 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.3, 139.2, 114.5, 87.1, 69.0, 60.4, 51.3, 41.9, 35.5, 34.5, 33.9, 29.6, 29.01, 28.99, 25.4, 21.3, 19.0, 14.6;

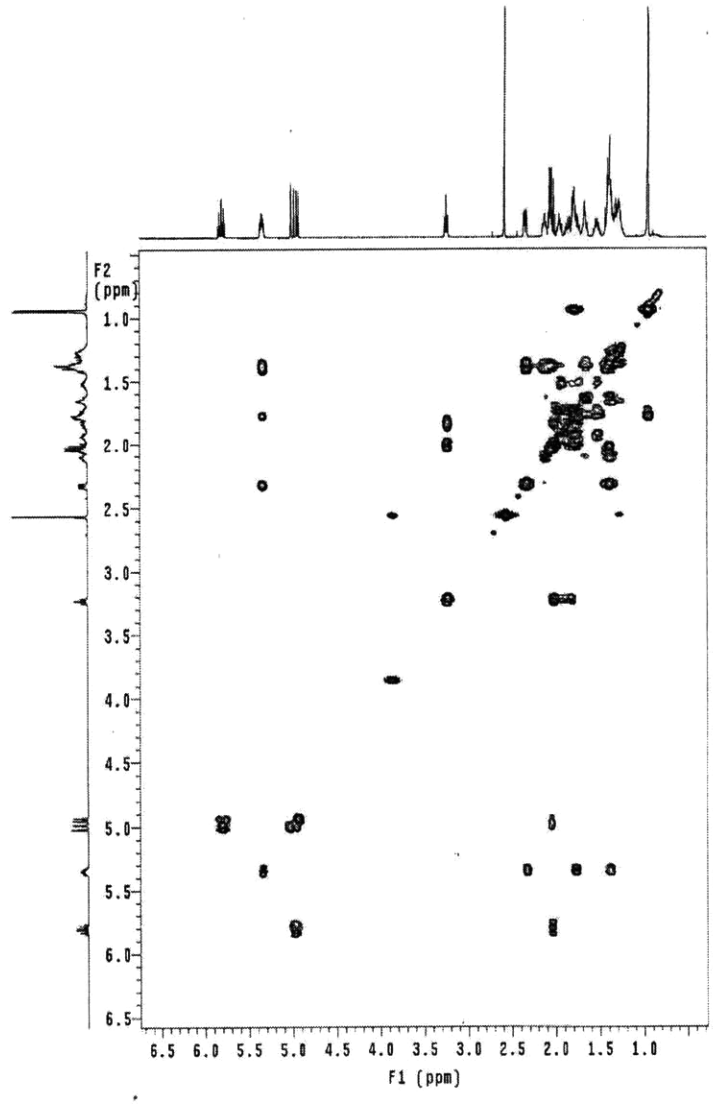
HRMS $[M+H]^+$ calcd for $C_{18}H_{31}NOS_2$: 342.1920, found: 342.1911; Anal. Calcd for $C_{18}H_{31}NOS_2$: C, 63.29; H, 9.15; N, 4.10. Found: C, 63.34; H, 9.27; N, 4.10. $[\alpha]^{24}_D$ +15.7 (*c* 1.0, $CHCl_3$)

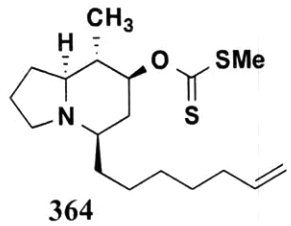

CH3
H
O
SMe
N
S
364
5.85
5.80
5.75
f1 (ppm)
5.35
5.30
f1 (ppm)
5.00
4.95
f1 (ppm)
2.32
f1 (ppm)
3.25
3.20
f1 (ppm)
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
f1 (ppm)
0.40
0.70
0.97
1.60
1.00
2.88
1.00
1.02
9.65
9.94
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

216.25
139.23
114.46
87.05
77.48
77.23
76.98
69.01
60.41
51.31
41.93
34.48
33.91
28.99
25.39
19.04
14.65
CH3
H
O
SMe
N
S
364
35.52
34.48
33.91
29.63
29.01
28.99
25.39
21.28
19.04
14.65
35
30
25
20
15
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

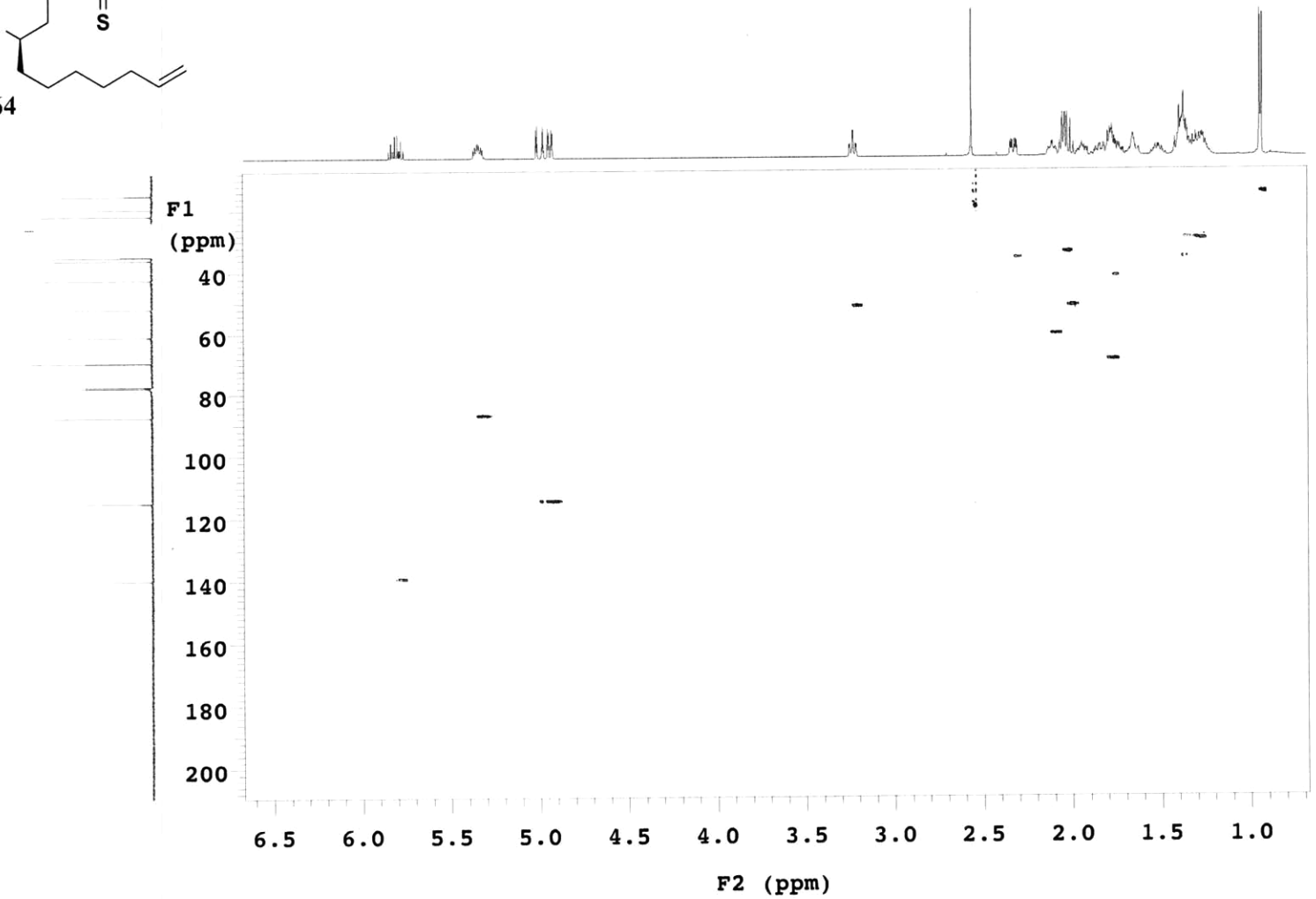

CH3
H
O
SMe
N
S

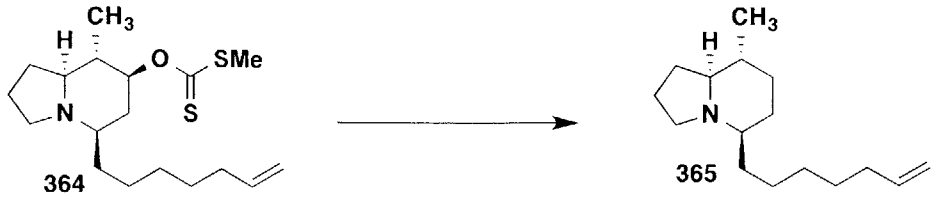
364


F2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F1 (ppm)


CH3
H
O
SMe
N
S

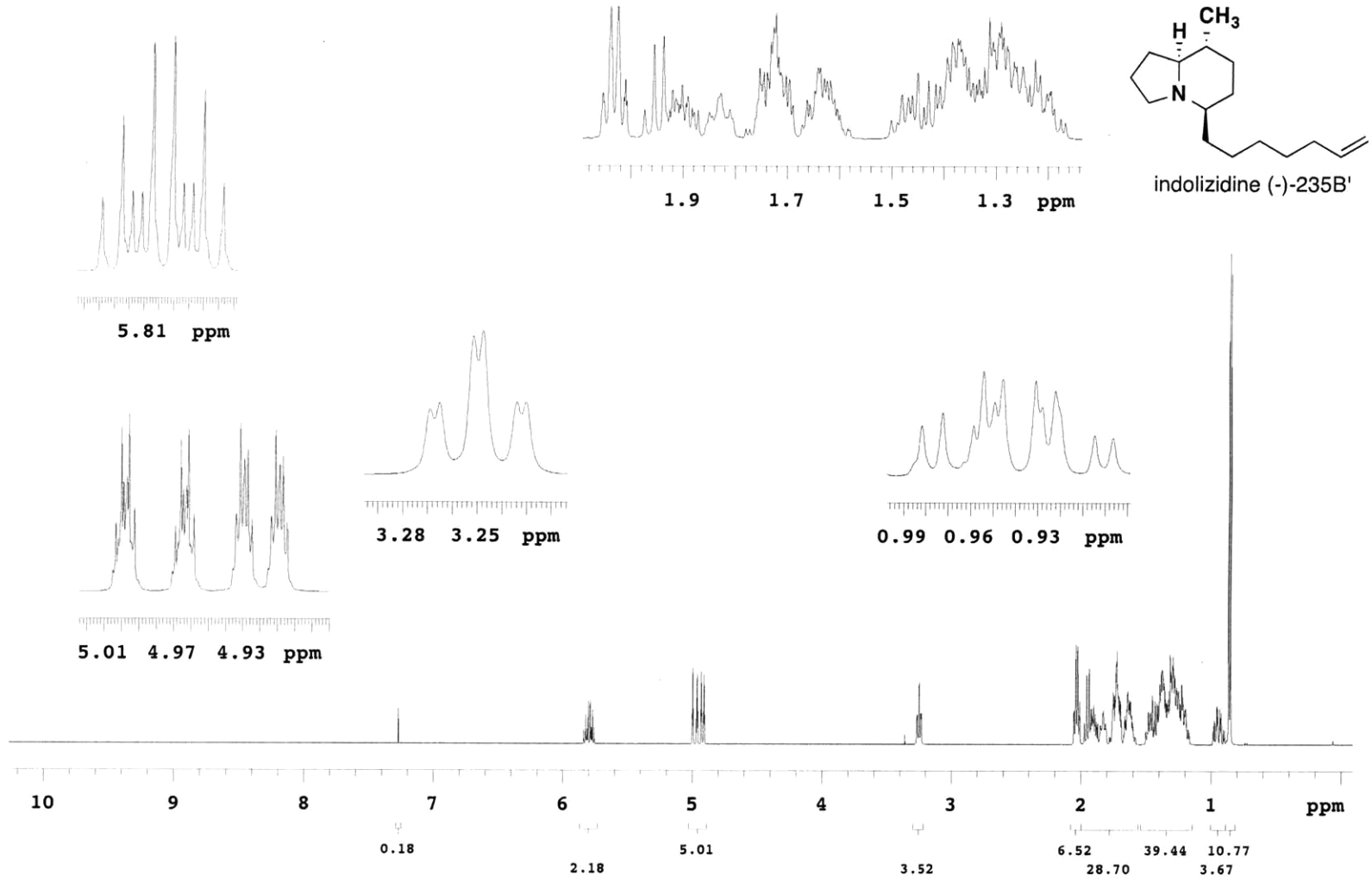
364

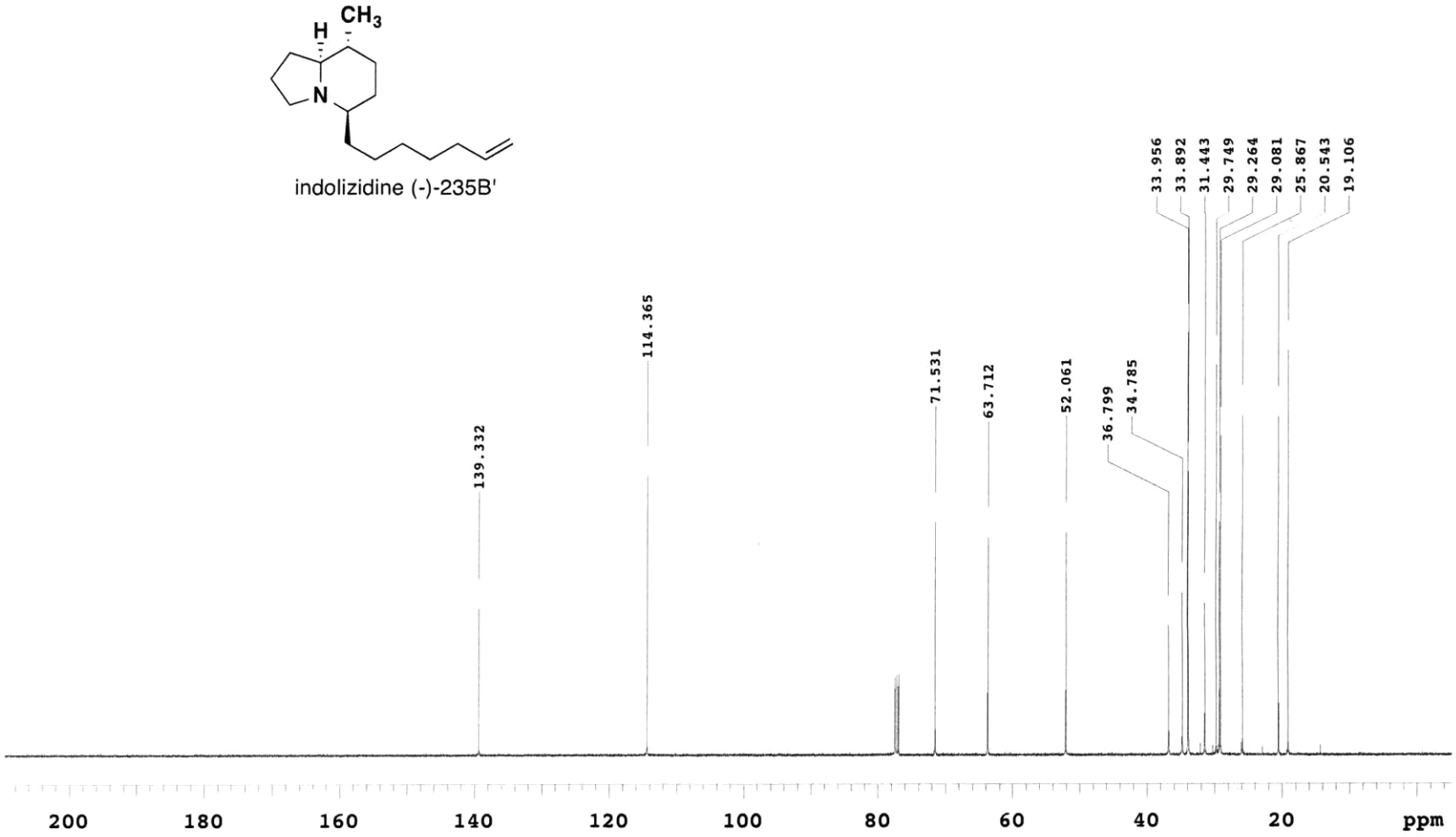

F1
(ppm)
40
60
80
100
120
140
160
180
200
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F2 (ppm)

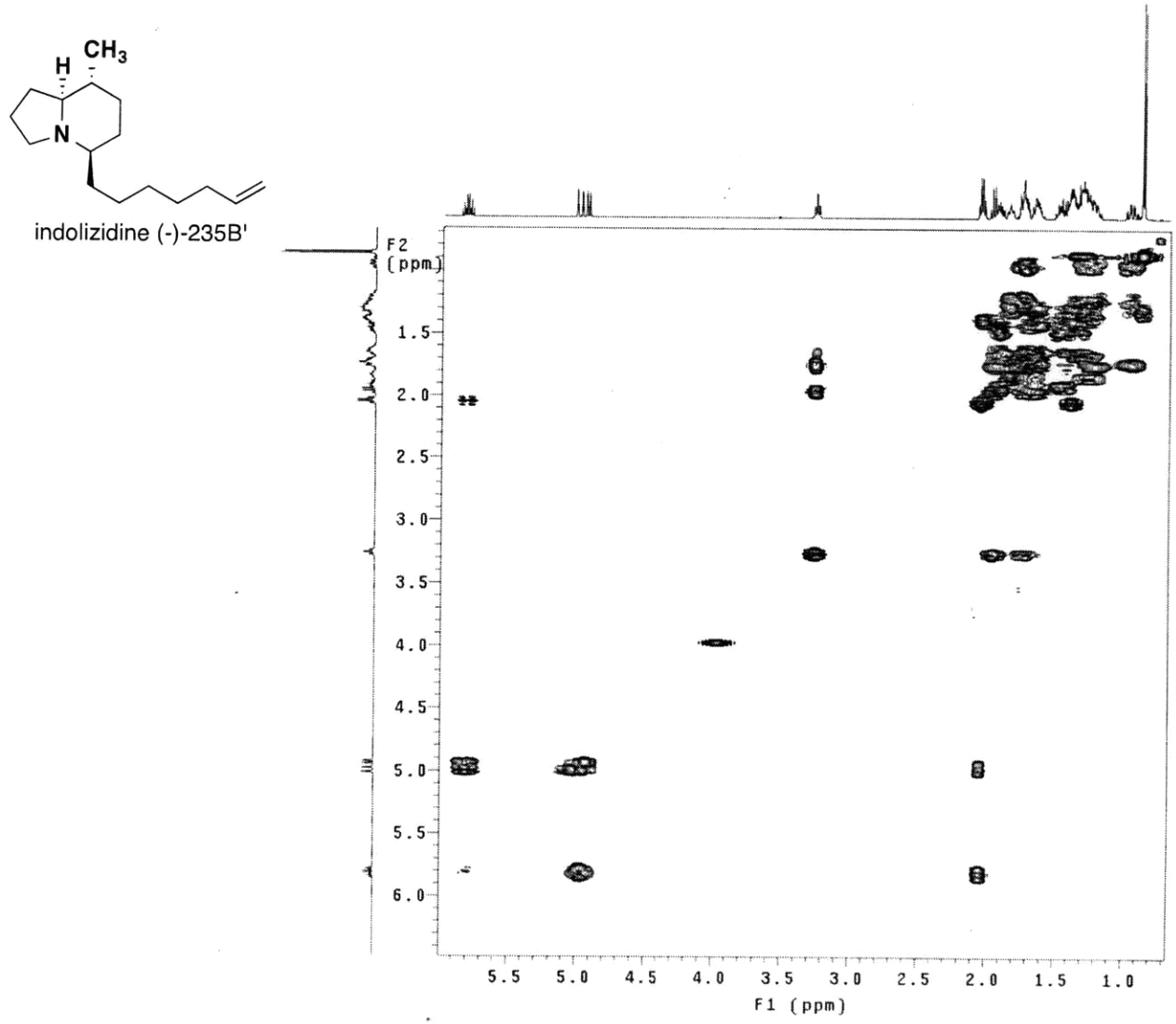


indolizidine (-)-235B'

Indolizidine (−)-235B′ (365). A 25-mL, two-necked, round-bottomed flask equipped with a glass stopper and a reflux condenser fitted with an argon inlet needle was charged with xanthate **364** (0.057 g, 0.17 mmol, 1.0 equiv), AIBN (0.011 g, 0.067 mmol, 0.4 equiv), and 4 mL of benzene. Bu_3SnH (0.088 mL, 0.096 g, 2.0 mmol) was then added in one portion via syringe. The reaction mixture was heated at reflux for 30 min. The yellow color disappeared, giving a colorless solution which was concentrated to give 0.145 g of a pale brown oil. This material was diluted with 10 mL of 1M aq HCl and washed with three 10-mL portions of hexanes. The aqueous solution was diluted with 13 mL of 1 M aq NaOH to give pH ≈14 and extracted with three 10-mL portions of $CHCl_3$. The combined chloroform layers were washed with 10 mL of water, dried over $MgSO_4$, filtered, and concentrated to afford 0.043 g of a pale yellow oil. Purification by column chromatography on 10 g of Al_2O_3 (elution with 2% EtOAc-hexanes) gave 0.028 g (70%) of **365** as a colorless oil: IR (neat): 3077, 2928, 2778, 1641, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.2, 10.3, 6.7 Hz, 1 H), 4.99 (ddt, J = 17.1, 2.1, 1.7 Hz, 1 H), 4.93 (ddt, J = 10.1, 2.1, 1.2 Hz, 1 H), 3.26 (ddd, J = 8.8, 8.8, 1.9 Hz, 1 H), 2.05 (dddt, J = 7.2, 1.6, 1.2, 6.7 Hz, 2 H), 1.96 (ddd, J = 9.1, 9.1, 9.1 Hz, 1 H), 1.91 (m, 1 H), 1.84 (m, 1 H), 1.70-1.79 (m, 3 H), 1.64 (m, 1 H), 1.17-1.51 (m, 12 H), 0.95 (m, 1 H), 0.87 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 114.4, 71.5, 63.7, 52.1, 36.8, 34.8, 34.0, 33.9, 31.5, 29.8, 29.3, 29.1, 25.9, 20.6, 19.1; Anal. Calcd for $C_{16}H_{29}N$: C, 81.63; H, 12.42; N, 5.95. Found: C, 81.60; H, 12.51; N, 5.82. $[\alpha]^{24}_D$ -69.1 (*c* 1.0, MeOH)


1.9 1.7 1.5 1.3 ppm
H
CH3
N
indolizidine (-)-235B'
5.81 ppm
3.28 3.25 ppm
0.99 0.96 0.93 ppm
5.01 4.97 4.93 ppm
10 9 8 7 6 5 4 3 2 1 ppm
0.18
2.18
5.01
3.52
6.52
28.70
39.44
10.77
3.67


H
CH3
N
indolizidine (-)-235B'
139.332
114.365
71.531
63.712
52.061
36.799
34.785
33.956
33.892
31.443
29.749
29.264
29.081
25.867
20.543
19.106
200
180
160
140
120
100
80
60
40
20
ppm


H
CH3
N
indolizidine (-)-235B'
F2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.5
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4.5
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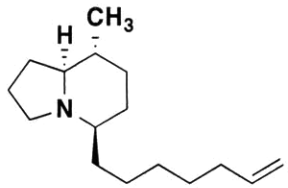
3.0
2.5
2.0
1.5
1.0
F1 (ppm)



indolizidine (-)-235B'